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EXPERIMENTAL MEDICINE

ON THE ACTION OF SUBSTANCES OF THE DIGITALIS SERIES ON THE CIRCULATION IN MAMMALS.

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PLATES XV–XXII.

The literature of the digitalis series is already so extensive that some apology may seem needed for adding yet another to the long list of papers on the subject. But except in a few more recent researches, the only method hitherto employed in studying its action on the mammalian circulation has been the manometric estimation of the blood pressure in the systemic arteries—a procedure which is entirely unsuited for giving satisfactory results as to the action of a drug on the heart. A number of other methods for registering the cardiac movements are, of course, in use in physiological laboratories, but few of these are adapted for pharmacological work, as here the changes appear more slowly and last longer than those produced by physiological means, and the apparatus must, therefore, be such as will permit of much longer observations than are generally necessary in the physiological laboratory. I had worked on the digitalis problem with several of these, among others, Martin's elimination of the peripheral circulation, the intracardiac pressure methods, and Stefani's method of using the pericardium as a plethysmograph, when Roy and Adami's work on the heart appeared, and I determined, after con-

sulting Professor Roy, to use the two methods there described. I may say at once that I have been perfectly satisfied with their apparatus, which is comparatively easily managed and gives results which are, I think, of great value in pharmacological work. I have made use of the apparatus with a number of other poisons besides those of the digitalis group, and have found it very satisfactory, not only giving details of changes in the heart hitherto unknown, but even registering the rate of the heart beat much more accurately than the manometer.

HISTORICAL.*

The action of digitalis has been the subject of investigation for the last century, but beyond the slowing of the heart observed first in man by Withering† and in the lower animals by Schiemann, there was little advance in ascertained fact until Blake, in 1839, discovered that the blood pressure was raised by the injection of the infusion into an artery. On the explanation of these two facts—the slowing of the heart and the increase in the arterial tension—the attention of workers in this field has been wholly concentrated until quite recently.

After the publication of Blake's paper there appeared, so far as I can discover, no experimental work until 1851, when Traube stated that the slowing of the heart could be removed by section of the pneumogastric in the neck, and ascribed it, therefore, to stimulation of the inhibitory centre in the medulla oblongata. He refuted by this experiment the statement of Stannius, which appeared in the same year, that digitalis acted only directly on the heart. Traube in the same paper announced that larger doses of digitalis, after stimulating, paralyze the vagus, and that the heart, thus released from control, increases to a rate far exceeding the normal. Eventually the motor system of the heart becomes paralyzed and standstill follows. Traube supposed that the vagus stimulation would lower the blood pressure, but did not make any experiments to ascertain if this was so. Lenz and Briquet in 1853 confirmed Blake's discovery of the rise in blood pressure during the period of slowing, and concluded that the latter was therefore not due to vagus action; while Winogradoff could detect no change in the blood pressure during the slowing, and therefore agreed with them in declaring that Traube's theory of vagus stimulation was untenable. In 1861 Traube published the results

* For the history of digitalis in the earlier part of this century I must refer to Schmiedeberg's paper in the *Arch. f. exp. Path. und Pharm.*, xvi, p. 149.

† References to literature will be found at the end of this article.

of a long series of kymographion experiments, which agreed with those of Lenz and of Briquet in showing marked slowing accompanied by an increase in blood pressure. This new phenomenon of increased blood pressure required some other explanation than the vagus stimulation, which he still looked upon as the chief action of the drug, and he therefore assumed that both the inhibitory and the motor nervous mechanisms of the heart were first stimulated and later paralyzed, the action on the inhibitory apparatus preceding that on the motor in each case. In this paper he acknowledges that section of the vagus does not always remove the slowing of the heart, and therefore assumes without further reason that the intracardiac inhibitory nerves are stimulated as well as the centre in the medulla.

While after 1861 the facts that digitalis in small quantities slows the heart by vagus action and raises the blood pressure, and in larger quantities quickens the heart and eventually lowers the pressure to zero, were not seriously disputed, every step of Traube's explanation has been hotly contested, and but few of them have stood the examination. Thus Klug denies that the inhibitory apparatus in the heart plays any role in the slowing, believing that it is due to stimulation of the centre in the medulla solely, and that it is entirely removed by section of the vagus, although he agrees with Boehm and Kaufmann that the irritability of this nerve is increased by digitalis. Others, however, such as Marmé, Ackermann, Bulgari, Schnabl, Popper, and Kaufmann, found that section of the pneumogastric did not prevent entirely the slowing, while Ackermann showed that the administration of atropin did so. *The slowing therefore seems to be due mainly to stimulation of the pneumogastric centre, but partly also to increased irritability (stimulation) of the terminations of the pneumogastric in the heart.*

Another question was raised by A. B. Meyer, who suggested that the vagus stimulation was not a primary action of the series, but was due to the increased arterial tension. This explanation was reiterated by Meyer and Brunton, but never received wide credence, and has been refuted by several observers, who observed very marked slowing accompanied by a low blood pressure (Kaufmann, Bubnoff, Popper, and others). In many cases in which large doses were applied I have observed a subnormal pressure accompanied by very marked slowing (see Experiment V). In fact, in most cases in which the diastolic pauses described later occurred, the blood pressure was little above, or even fell below, the normal height. *The action on the vagus centre therefore seems to be a direct one,* or at any rate is not an effect of the increased blood pressure.

Traube's explanation of the acceleration of the dog's heart in the later

stages of digitalis action—the paralysis of the pneumogastric—has proved insufficient, for Ackermann found it to occur in experiments in which the pneumogastric influence had been removed from the first by atropin. On the other hand the vagus is believed to have lost control of the heart in the stage of acceleration, for electrical stimulation has no effect (Ackermann, Klug, Bubnoff, Kaufmann, etc.), although Marmé disputes this. In the rabbit the inhibitory action is much less marked in digitalis experiments, and, there being scarcely any acceleration beyond the normal (Klug), stimulation of the vagus is followed by slowing up to the end of the experiment (Marmé, Klug). Some other factor has therefore to be assumed than the mere paralysis of the inhibition, and Klug therefore maintains that the quickening is due, at any rate partly, to the increased irritability of the motor ganglia of the heart, while Bubnoff considers the acceleration to be due to paralysis of the inhibitory apparatus together with stimulation of the accelerator system. In view of the fact that the heart muscle is undoubtedly acted on by this group, it seems to me unnecessary to assume any action on the more or less hypothetical motor ganglia of the heart. Besides, as I have satisfied myself, the same increase in irritability occurs in the non-ganglionated apex of the frog's heart, which shows a much greater tendency to beat if suspended in blood to which digitalis has been added than in unpoisoned blood (cf. Tschistowitsch). One effect of increased irritability of the cardiac muscle was shown by Harnack and Witkowski to be a diminution of the inhibitory power of the pneumogastric; and Schmiedeberg and Koppe, and later Boehm, showed that in the frog's heart digitalis tends to remove the inhibitory standstill of muscarin. I should suggest, therefore, that *although the fatigue of the inhibitory apparatus may in part account for the acceleration of the heart in the later stages of digitalis poisoning, a factor of greater importance is the increased irritability of the heart muscle,* which refuses to be further controlled by inhibitory impulses. As I shall show presently, the same two opposing factors are in action throughout the first stage, and the acceleration merely indicates that the muscular action has overcome the inhibitory. In the dog the irritability is generally so much augmented that the heart is accelerated beyond the normal rhythm, and electrical stimulation of the vagus is entirely without effect on the rate of the ventricle. In one or two experiments, however, I found distinct slowing and diastolic pauses produced by vagus stimulation in the last stage of poisoning; and in the others, although the rate was not changed by it, a distinct tendency towards the diastolic position was caused in the ventricle and a lessening in the size of the beats of the auricle. In some animals, such as the

rabbit, the increase in the irritability is less marked than in the dog, and the heart may still be slowed by vagus stimulation.

It does not seem to have occurred to Traube, even in his later work on the subject, that any other cardiac mechanism except the nervous ganglia was affected by digitalis. This was owing to the fact that his attention was confined to the mammalian circulation, and the most important advance which we owe to the numerous researches on the action of digitalis on the frog's heart is the knowledge that the chief results are due to the changes produced in the muscular and not to those in the nervous mechanism. Boehm seems to be the first who emphasized this point, and his view has found the support, I think, of almost all later writers. The details of the changes in the heart muscle have been studied by Schmiedeberg, who brought forward the theory that the chief alteration was an increase in the elasticity of the heart muscle. This explanation has received wide acceptance, but has been rendered somewhat doubtful by Roy's work on the elasticity of the heart.

The cause of the rise in blood pressure after the administration of digitalis has been no less a matter of dispute. Blake attributed it to a contraction of the peripheral vessels, and this forgotten explanation was again revived by Marmé and supported by Brunton, Brunton and Meyer, Mégevand, Siergiejenko, v. Schroff jun., Legroux, Gourvat, Ackermann, Brunton and Pye, Rummo and Ferranini, Bubnoff and Klug.* On the other hand Boehm, Görz, Popper, Schmiedeberg and his pupils (*e. g.* Williams and Koppe) have always maintained that the rise in pressure is due to the increased strength of the heart and that the vessels have here little or no influence on the change. Their arguments have been, however, very largely drawn from the behavior of the frog's heart, and this differs so greatly from that of the mammalian under digitalis that too great importance must not be given to deductions from it. While I do not wish to enter into the literature of the action of this series on the cold-blooded heart, I may remark that although the individual contractions are generally acknowledged to be strengthened by digitalis, the experiments of Donaldson and Stevens show that less blood is thrown out per minute than in the normal condition, so that even in those animals the rise in blood pressure cannot well be due to the cardiac action.

The further question arose as to the part played by the vaso-constrictor centre in the rise of pressure, and here Traube and Boehm were at first

* Since this paper was sent to press, a further article by Brunton and Tunnicliffe has appeared supporting this point of view. *Journ. of Physiology*, xx, 354.

at one in denying that digitalis could produce an increase in the tension after the spinal cord had been cut. Boehm, however, soon recognized that the rise in pressure is, at any rate in part, independent of the vaso-constrictor centre, and gave expression to his change of view in the dissertation of his pupil Görz, thus confirming the statement of Ackermann in this particular, while stoutly maintaining that the peripheral vessels are not contracted. Some few other writers contend also for the action on the vasomotor centre (Marmé, Mégevand, Siergiejenko, Gourvat, and lately Dotschewski), but most workers on the subject allow that a marked increase in arterial tension occurs even after division of the cord, although the question is still unsettled as to whether the centre may not participate to some extent in the rise occurring in the uninjured animal (Klug). A further argument for the vascular action of the group has been found in the behavior of the mammalian vessels observed on direct examination. Legroux, Gourvat, Ackermann, Brunton and Pye, Bubnoff and Klug maintain that the vessels can be seen to contract; Brunton and Meyer express themselves as uncertain, while accepting the vascular action on other grounds; Görz and Koppe could make out no contraction, while Popper was satisfied that the vessels were redder after strophanthin than before it. Several of the supporters of the vascular action did not observe any narrowing of the calibre of the vessels of the frog's web. A very large majority, then, seem to entertain the belief that the rise of pressure is to a large extent due to action on the peripheral arteries, although they almost all admit that the increased activity of the heart also plays a part in the phenomenon. The medullary centres were, however, shown not to be essential to the rise in pressure, and by a process of exclusion it could be shown that the peripheral arteries were the seat of action to a large extent. Some, however, not satisfied with this reasoning, examined the calibre of the peripheral vessels and found them narrowed even after section of the vasomotor nerves leading to them (Brunton and Pye, Bubnoff and Klug), while Gourvat found narrowing to occur only so long as the vessels were in connection with the governing centres.

A mass of other evidence has accumulated for the action of these drugs on the peripheral vessels. Thus Kobert, Thomson, Bubnoff, and Talma and v. der Weyde found that the quantity of blood passing through the kidneys and other "surviving" (überlebende) organs is very much diminished by the administration of any of the series. The objections have been raised that these organs were not normal and that larger quantities of the drug were added to the blood than could circulate in it in the living animal. These objections cannot, however, be made to the

method of Bradford and Philipps, who measured the amount of blood in the kidney by means of Roy's oncometer and found that digitalis lessened that organ considerably, thus showing that the renal vessels are narrowed. As regards strophanthin, they state that they observed little effect on the calibre of the renal vessels; but in one of the tracings given, a lasting, though small diminution in the size of the kidney is to be seen, while in another the drug seems to have had no effect on the blood pressure and the kidney enlarges. Delsaux is said to have found also that strophanthin does not change the volume of the kidney measured by the oncometer. There is a very general opinion that strophanthin differs from digitalis in possessing but little action on the vessels, and it is not unlikely that the members of the series vary in this respect. Work on this question is at present being carried on in my laboratory, and I hope to give the results in a future communication. However that may turn out, I think the evidence is overwhelming that *the rise in pressure in the arteries is to a considerable extent due to action on the muscular walls of the arterioles.*

The fall in arterial tension towards the close of the action is almost universally ascribed to failure of the heart. Brunton suggested that the arterioles dilated owing to paralysis of their walls after the primary contraction, but Bubnoff has shown that in "surviving" organs no dilation occurs even with very large quantities of the drug and after long experiments.

Several observers (Stannius, Ackermann, etc.) found the heart non-irritable after the thorax was opened, but Klug maintains that this is true only for dogs, in which the unpoisoned heart loses its irritability very soon after standstill, and that in rabbits the irritability lasts very much longer.

Many observers have described at length the variations of the blood pressure in what is known as the irregular stage. These are no doubt of interest, but I do not think it possible to draw correct inferences from them as to the state of the heart, as many have attempted to do. I shall therefore not discuss them here, but refer those interested to Boehm's paper, in which they are described at some length.

In concluding this account of the literature concerning the rise of blood pressure, I must state that most observers, while holding that the increase is due mainly to one or other cause, concede that it may be in part due to all three—heart, vasomotor centre, and peripheral vessel walls. There is reason to believe that the different members of the series do not all act to the same extent upon these three factors. Thus while the vascular action of digitalis is supposed by the majority of observers to be

to a considerable extent responsible for the increased tension, strophanthin, as mentioned above, is believed to cause it more by its direct action on the heart.

Besides the examination of the blood pressure in the systemic circulation, some other methods have been used to determine the action of this group on the circulation. Thus Ackermann measured the venous pressure in the iliac veins and found it practically unchanged by digitalis, while Popper found the venous pressure fall as the arterial rose after strophanthin injection. If the arterial pressure is not much raised and the heart is very much slowed, the venous pressure may rise. From these results he draws the somewhat dangerous inference that the cause of the increased arterial pressure is the action on the heart.

Ludwig's Stromuhr has been applied by Kramnik and by Hemmeter, of whom the former found small quantities of digitalis quicken and larger quantities slow the circulation, while Hemmeter found the velocity uniformly lessened. Kaufmann, using the hæmodromograph of Chauveau, found the velocity of the blood current lessened during the stage of increased arterial blood pressure.

A good deal of work has been done of late years on the effects of this series on the pulmonary circulation. Thus Popper found the pressure in the pulmonary artery only very slightly increased in the one experiment which he performed with this method. Bradford and Dean found also merely an insignificant increase in pressure in the pulmonary artery after strophanthin, while digitalin caused a much more marked increase. Tschistowitsch found, however, the vessels of the surviving lung much narrowed by hellebore. Openchowski observed that the pressure in the pulmonary artery first fell and then rose again somewhat above the normal. These changes, however, he considers due to the action on the systemic circulation, and not to any direct influence on the right heart or pulmonary circulation. In fact the whole of his paper is devoted to showing that under helleborein the pulmonary circulation and right heart show no abnormalities which may not be considered indirect results of the changes in the systemic circulation, and to explaining the absence of the symptoms of direct action on the right ventricle. In order to do this he puts forward the extraordinary theory that the right heart is acted on, but that the effects of the drug are masked by the simultaneous contraction of the right coronary artery, which by producing inanition of the right ventricle neutralizes the stimulant effect of the drug. Why this action should be confined to the right coronary he does not explain. He supports his position by several arguments, such as that, if the normal heart be excised, the left ventricle ceases to beat

before the right, but in the heart poisoned with helleborein the sequence is reversed. On direct inspection the right ventricle beats twice as fast as the left, and the former is dilated while the latter is contracted. This difference in the rhythm can also be seen in blood pressure tracings from the pulmonary and carotid arteries. The left coronary artery was distended with blood, while the right seemed to contain less than before the injection. Ecchymoses could be found in the left ventricle, while none could be found in those parts of the right ventricle supplied exclusively by the right coronary.* Lastly, the vagus action on the right ventricle seemed weakened by helleborein. Bayet is said to support the assertions of Openchowski as to the dissociation of the right and left ventricles under digitalis, but I have been unable to obtain either his original paper or even a satisfactory abstract of it.

Knoll, working with the same methods and the same drug as Openchowski, came to very different results. These two seem the first to use the method of direct inspection of the heart. Unfortunately both injected such large quantities of the drug that they missed the most important part of the action—the first or therapeutic stage. This was natural enough in Knoll's case, because he wished to investigate, not the therapeutic action of the drug, but what is known as the irregular stage. Openchowski, on the other hand, made deductions as to the therapeutics of the drug without apparently having observed the therapeutic stage of its action. Knoll explains the variation in rhythm in Openchowski's tracings as an illusion caused by the one artery having a bigeminous pulse due to two independent contractions of the ventricle, while the other shows two full pulse waves. He observed no difference in the rhythm of the two sides of the heart. The left ventricle does not necessarily beat longer than the right, but may cease simultaneously with or even in advance of it. No rise in pressure occurs in the pulmonary circulation at the time of the marked increase in systemic tension. He is the first writer to mention the periodic character of the heart's action in the later stages of poisoning, and his paper is in fact almost wholly devoted to the "Incongruenz" or absence of correspondence in the tone and strength of contraction of different parts of the heart at any one time. The periodic stage observed by him is marked by intervals of excessive diastolic dilatation, alternating with periods of lessened and imperfect dilatation. In other cases a series of small contractions alternates with another in which the movements are very large, and

* Bubnoff found extravasations under the endocardium in both ventricles, although more distinct in the left, as well as in other organs. Orfila found ecchymoses in both cavities.

several other forms of periodic variation are described by him. This periodic irregularity may occur in any division of the heart, while the others beat fairly regularly, or two parts may be observed to be undergoing the same form of irregularity at the same time, although the large contractions of the one correspond in time with the small ones of the other. It is impossible to do justice to Knoll's paper without reproducing his tracings, and I must therefore refer those interested to the original.

There seems, then, a consensus of opinion that *the pressure in the pulmonary artery is not changed to nearly the same degree as that in the carotid* by the administration of several of these drugs, although some of them at any rate increase the pressure to a small extent.

A few observers have recently used more direct methods of registering the movements of the heart. Of these Tschistowitsch found that in the mammalian heart, isolated from its vascular and nervous connections, helleborein increased the activity of the heart and the amount of blood expelled by it in a unit of time, but he does not go into any detail as to the changes observed.

Kaufmann and Rolleston investigated the endocardial pressure under members of this series by introducing sounds into the different cavities, Kaufmann into the right heart and Rolleston into the left. The diastolic and systolic auricular pressure, according to the former, is increased for a time and then decreases, both changes being due to the contraction of the peripheral vessels. The ventricular pressure in systole and diastole increases simultaneously with the auricular, but the systolic remains augmented for a much longer time, while the diastolic ventricular pressure falls at the same time as the auricular. The increase in diastolic pressure in the ventricle he supposed to be due to the heart failing to relax sufficiently. The rise in the ventricular pressure curve at each contraction is more rapid and the fall slower than normal. Rolleston found that strophanthin increases the maximum pressure in the left ventricle during the period of slow rhythm. The ventricular dicrotic notch is increased, as he considers, owing to the increased rapidity of the circulation and the increased output of each contraction of the heart. Zerner found a fall in the pressure in the left auricle accompany the rise in the aortic pressure. Stefani and Gallerani assert that after digitalin the heart can relax against a greater pressure in the pericardium than normally. Stefani found later that this result persisted after section of the vagi, and concluded that it is due to a direct action on the cardiac muscle. He was apparently ignorant of the fact demonstrated by Ackermann and others that digitalis acts on the peripheral inhibitory apparatus and that

it is not sufficient therefore to divide the vagi. Roy and Adami describe the first effect of strophanthus as an increased force and efficiency in the contractions of the papillary muscles, without any, or with only very slight, increase in the force of the contraction of the ventricular walls. Large doses of strophanthus weaken the ventricular wall, but to a much greater extent the papillary muscles, which may cease to move while the wall still contracts. Before this occurs, dissociation of the contractions of the two parts may occur, the papillary muscles sometimes contracting with the ventricular wall, sometimes failing to contract, and sometimes contracting twice for the single contraction of the ventricle.

After I had commenced my work on this subject a new paper by Knoll appeared, describing the results obtained by a method of registering the movements of all four divisions of the heart simultaneously. By the use of this somewhat inaccurate apparatus he found that helleborein causes arhythmia, increase in the extent of individual systoles or diastoles, and periods of augmented and diminished activity of movement. Each of the four divisions may show variations quite independent of the others, and no one feature can be said to occur exclusively in one division. The auricles generally cease contracting before the ventricles. The purpose of this paper, like that of his former one, is to show the "Incongruenz" of the four divisions of the heart, and the author contents himself with appending a large number of tracings without attempting either to describe or to explain them. I am pleased to find in his tracings the same features as in my own during the second or periodic stage, but, as in his former paper, he overlooks entirely the characteristic changes of the heart in the earlier stages of the action of these remedies.

EXPERIMENTAL.

A considerable number of my observations were made without the use of apparatus, by opening the thorax and exposing the heart, of course with the use of artificial respiration. The drug was then injected into the jugular vein, and the changes that occurred in the cardiac movements were carefully noted. These experiments were made on cats and rabbits, but the dog's heart may also be observed quite satisfactorily while the myocardiograph is attached, and I have always controlled the tracings of the levers by observing the heart directly. The changes in the mammalian heart are, however, much more difficult to follow than those in the slowly contracting heart of cold-blooded animals, and I do not think that I could have satisfied myself as to their course without the aid of the graphic method. The apparatus used were the myocardiograph and cardiometer of Roy and Adami. The former may be described shortly

as an apparatus with which the distance between two points on the heart's surface and their movements relative to one another are recorded, while the latter measures the volume of the heart in its successive phases, and therefore records the amount of blood expelled from the heart. In my myocardiograph experiments I have used dogs and cats. In the latter, however, the results are often somewhat unsatisfactory, as the instrument seems to injure the muscle somewhat, and I have only done a few experiments to satisfy myself that the results with the myocardiograph are the same in both animals. The description of the results of the myocardiographic work is therefore to be considered as derived from observations on the dog's heart. For the cardiometer, on the other hand, I found the cat's heart very suitable and have used this method on these animals exclusively. I attempted to attach this instrument to the rabbit's heart, but found the pericardium too delicate.

In all my work I used morphine as narcotic, except for rabbits, where urethane was used. In a good many I subsequently gave acetone chloroform as advised by Abel, the combination of this and morphine giving excellent results. The quantity given must, however, be carefully noted, as large doses seem to weaken the heart. In some cases, instead of acetone chloroform I gave a small quantity of chloroform in the beginning of the experiment, the large dose of morphine sufficing afterwards for complete narcosis. In a few experiments curare was given to eliminate any possible muscular influence.

The apparatus was applied as described by Roy and Adami, artificial respiration being supplied for small animals by an air pump and Runne's interruptor, while for large dogs the ordinary hand bellows were made use of.

In cats the poison was injected by the jugular, in dogs by the saphenous vein, generally in 0.1 per cent, in some cases 0.2 per cent solution. Most frequently strophanthin was used (supplied by Boehringer), but several experiments were made with digitalinum verum (Boehringer), antiarin (Boehringer), digitalin (Trommsdorf), erythrophlœin hydrochlorate (Schuchardt), and convallamarin (Merck). I satisfied myself that the action of all of them on the cardiac muscle is identical in kind, although varying in strength. Thus digitalinum verum and erythrophlœin proved the weakest of all, while antiarin and strophanthin were the strongest, and convallamarin and digitalin occupied an intermediate position. It has been shown that the different members of this series probably diverge considerably in the strength of their vascular as compared with their cardiac action. Another point in which they also differ is the relative degree to which each acts on the inhibitory apparatus and the cardiac

muscle. Thus erythrophlœin undoubtedly acts less on the cardiac muscle and more on the vagus centre than any of the others that I have examined, and probably the others vary also in the extent to which they stimulate those agencies. A comparison of the series as regards their action on these three points—the cardiac muscle, the vessels and the inhibitory apparatus—would undoubtedly be of the greatest therapeutic importance, but would involve the use of a much greater number of animals than I have at present at my disposal.

To avoid constant repetition in the account of the literature I have given, I have assumed (what was unknown until much of the work quoted had been completed) that what held true of one member of this series was in general terms true of all, and have therefore not generally mentioned the particular drug which each observer used, but this is noted in the references given at the end of my paper. In the same way I shall use "digitalis" or "digitalis series" throughout, although the experiments on which the statement is founded may have been performed with some other member of the group.

In descriptions of the action of digitalis the phenomena are generally divided into four stages, according to the rate of the heart and the height of the blood pressure. In my tracings, however, these four stages are not by any means distinctly marked off, and I shall divide the action into two stages, according to the condition of the ventricle. In the first stage one of the most marked features is the stimulation of the pneumogastric, in the second the acceleration and the periodic changes in the strength of the contractions, and I shall therefore call them the vagus stage and the periodic or irregular stage. It must not be supposed, however, that the vagus stimulation is the only feature of the first stage, for the heart muscle is also acted on directly, and the variations in the tracings of this stage are due to the differing degrees to which these two factors are in activity in different hearts. So in the second stage the periods are only one of many features. The auricles do not in many cases undergo acceleration at the same time as the ventricles, but in order to simplify the description I shall consider the acceleration of the ventricle the indication of the commencement of the second stage.

VENTRICULAR CHANGES IN THE FIRST STAGE, OR STAGE OF VAGUS ACTIVITY (MYOCARDIOGRAPHIC TRACINGS).

The action of this series on the ventricle sets in only one-half to two minutes after the injection, if small quantities are used, and is marked by *slowing of the beat and increased excursions towards systole and generally towards diastole.* (Plate XV, Fig. 1, *a* and *b*, and Plate XVI, Fig. 4, *a* and *b*.)

Experiment I, April 8.—Large dog narcotized by morphine and curara. Myocardiograph attached to the left ventricle.

Time.	Number of contractions in 10 seconds.	Height of systole from base line.	Height of diastole from base line.	Length of excursion of lever.
5.6	35	26 mm.	38½ mm.	12½ mm.
5.10—5.10¼	1 mg. strophanthin injected into the jugular vein.			
5.10.30	35	27	39	12
5.11	33	26½	43	16½
5.11.20	28	25	45	20
5.11.40	24½	23	44	21
5.12	22	20	43½	23½

In this experiment the rhythm of the heart is slowed, the height of the systole from the base line is diminished, *i. e.* the systole is more complete while the distance of the diastole from the base is increased, *i. e.* the relaxation of the heart is very much greater. The excursion of the lever is almost doubled in length.

Experiment II, April 12.—Dog of medium size narcotized with morphine only. Myocardiograph attached to the left ventricle.

Time.	Number of contractions in 10 seconds.	Height of systole from base line.	Height of diastole from base line.	Length of excursion of lever.
4.22	16	48 mm.	63½ mm.	15½ mm.
4.22.15	Injection of ½ mg. strophanthin into the vena saphena.			
4.22.30	15	50	63	13
4.24	15	48	62	14
4.26	15	45½	61½	16
4.27	15	42½	61½	19
4.29	14	40	59½	19
4.31	13	37	57	20
4.32½	12½	37	57	20
4.33½	Occasional pauses in diastole.			
4.35	4½	40	64	24
4.36	Both vagi cut.			
4.37½	14	36	55	19
4.38	16	29½	52½	23

Here the slowing at first was comparatively slight, the systolic contraction was considerably increased, while the diastole was actually less perfect than before the injection. As the slowing became very marked the diastole became more complete, the systole less so. On section of the vagi the rhythm soon returned to the normal, while the diastoles became less perfect than before, and the contraction reached an extreme degree.

The slowing of the rhythm is almost constant. In some cases, however, it did not occur, although the vagus, as tested by electrical stimulation, seemed to possess its usual action. The slowing is progressive, the rate at first scarcely departing from the normal, but later decreasing frequently to one-half or one-quarter, or even less, of that before the injection.

The increase in the contraction sets in generally about the same time as the retardation, and like it progresses slowly. The degree of relaxation reached by the heart muscle is somewhat more variable. In the majority of my tracings it is increased as in Exp. I, but not infrequently it is not only not increased but actually diminished, as in Exp. II. When it is increased the change is often small, and in fact is generally smaller than in Exp. I. To a certain extent the slowing and the increase in diastole run parallel to each other, the latter being especially marked when what will be later described as the pause phase sets in, but this rule is not by any means without exception, marked increase in diastole being sometimes observed with comparatively slight retardation.

The time at which those three features appear varies considerably, in some cases the slowing and increased diastole preceding the increased contraction, in others the opposite sequence occurring. The extent to which each is developed also presents marked differences, in some hearts the slowing being the most prominent feature, in others the increase in diastole, and in others the increased contraction. The increase in systole and diastole of course leads to a much greater excursion of the lever, and the characteristic of this period is therefore a slow, very large beat. (Plate XV, Fig. 1.)

The cause of these three modifications of the contraction is not

difficult to determine. The *slowing*, as was first shown by Ackermann, is *due entirely to the inhibitory apparatus*, and is altogether absent in hearts in which this has been paralyzed by atropin. (Plate XV, Fig. 2.) The *increase in systole* is undoubtedly due to *direct action on the cardiac muscle.* It occurs in atropinized hearts at least as markedly as in those in which the inhibitory apparatus is in play (Plate XV, Fig. 2), and is therefore entirely independent of the latter, which, moreover, as Roy and Adami have shown, increases the amount of residual blood and causes a less complete systolic contraction. It must be remembered that the tracings do not show the full extent to which the contractility of the heart muscle is altered by these drugs, for, as has been shown by these authors, an increase in the aortic pressure is, *ceteris paribus*, accompanied by a less perfect systole of the left ventricle. Digitalis raises the aortic pressure very markedly at this stage, yet instead of a less perfect we find a much more perfect contraction of the ventricle.

The position of diastole after digitalis seems to be determined by the interaction of several factors. The influence of the inhibitory mechanism is seen by the result of the section of the vagus in Exp. II, as well as by the fact that after atropin the dilatation is never increased by digitalis. The increased dilatation generally seen must therefore be due to the inhibitory stimulation. On the other hand the diastole may either reach its usual extent or be less perfect than before the administration of the drug, whether atropin has been previously administered or not (Plate XV, Figs. 2 and 3), and I can give no explanation for this variation save that possibly, when the heart muscle is weakened and relaxed from any cause such as by large quantities of the narcotic, digitalis may lessen its relaxation, while, if the muscular tone of the heart is fairly normal, it is not changed by the direct cardiac action of this series.

Experiment III, May 25.—Medium-sized dog narcotized with morphine and acetone chloroform. Atropin injected until the vagus was paralyzed, as seen by electric stimulation. Myocardiograph attached to the right ventricle, the manometer to the left carotid.

Time.	Number of contractions in 10 seconds.	Height of systole from base line.	Height of diastole from base line.	Length of excursion.	Blood pressure in mm. mercury.
11.1	31	45½ mm.	84 mm.	38½ mm.	92-94
11.1½	1 mg. strophanthin injected into the vena saphena.				
11.2	31½	45	84	39	94
11.3	31	42	84	42	106
11.4	31	38	84	46	132
11.5	31	35½	84	48½	140
11.6	31	35½	84	48½	138

In this experiment the rhythm of the heart remains unchanged, and the degree to which relaxation occurs is also constant. The contraction, on the other hand, is much more perfect than before, and with it of course the length of the excursion increases.

In tracings of this stage taken on a more rapidly revolving drum some additional features may be made out. (See Plate XVIII, Fig. 6, *a*, *b*, *c*.) The slowing is now seen to be due mainly to the prolongation of the diastolic pause. The actual contraction of the muscle is unchanged, or slightly shorter in duration, while the relaxation presents no points of difference as regards speed from the normal. The time spent in a condition of contraction is considerably lengthened. This is evident on the first glance at the tracings. I have found, however, considerable difficulty in estimating the amount of the prolongation, as it is very difficult to decide at what point systolic contraction ceases and the pause in contraction begins.

Experiment IV, November 22.—Medium-sized dog narcotized by morphine and acetone chloroform. Myocardiograph attached to the left ventricle. The numbers indicate the length in millimetres on the tracing during which each phase lasted.

Time.	Duration of actual contraction.	Duration of rest in full contraction.	Duration of relaxation.	Duration of pause in diastole.
3.11½	6	6½	2½	2
3.12	2 mg. strophanthin injected into the saphenous vein.			
3.13	6	7½	2½	2½
3.14	5½	7½	2½	2½
3.15½	5½	8	3	5½
3.16	5½	9½	2½	11
3.16½	6	11	2½	10-14½

In this experiment, while the time during which the lever was in actual movement, ascending and descending, remains practically

unchanged, the time during which the heart remains in complete contraction increases from 6½ to 11, or almost 70 per cent. On the other hand the time spent in complete diastole increases from 2 to 10–14½, or about 5 to 7 times.

As the time occupied in actual contraction and relaxation is practically unchanged by digitalis, I have often estimated the prolongation of the systole by measuring the interval between the departure from, and the return to, the position of relaxation.

Experiment V, December 16.—Small dog narcotized with morphine and acetone chloroform. Myocardiograph attached to the right ventricle.

Time.	Rate in 10 seconds.	Distance of systole from base line.	Distance of diastole from base line.	Duration of complete contraction.	Duration. of diastolic pause.	Blood pressure.
3.25	18	64 mm.	102 mm.	2½	1½	54
3.28	1 mg. of strophanthin injected into the vena saphena.					
3.30	17½	59	103½	2¾	1¾	84
3.32½	15	59	104	3	3	90
3.38	9	60	104	3½	10	68
3.45	6	60	104	4½	17	36
3.48	4	59	104	6½	22–35	36

In this experiment, in which extreme slowing occurred, the duration of the contraction increased from two to three times, while the diastolic pause was about twenty times the normal length. The blood pressure, it may be noted, is subnormal at the time of greatest slowing. As the latter increased the size of the pulse wave became rapidly larger, although the heart excursions remained unchanged in size in the latter half of the experiment.

The cause of the prolongation of diastole is evidently the activity of the inhibitory mechanism. It is entirely absent in the atropinized heart. On the other hand the prolongation of the systole might be supposed to be due to the action on the muscle, as it is the most characteristic feature of the action on the cold-blooded animals. I have, however, failed to find it in the tracings from atropinized hearts, and am inclined to consider it the result of the slowing. In the slowing of the heart due to vagus stimulation the duration of systole is also greater than normal, and in tracings taken from an unpoisoned heart, in which the slow ventricular rhythm was produced by Wooldridge's

method, the same prolongation of the stage of complete contraction was observed.

The phenomena described as yet are those produced by moderate quantities of the drug and correspond to those seen in its therapeutic use. This stage lasts for a long time in cases in which the proper quantity has been injected, and the features remain with but little variation so long as other factors besides the poison do not come into play. If larger doses be used the features of the tracing change after a very short time, a more marked form of vagus activity not infrequently making itself apparent. This is heralded (Plate XVII, Fig. 5, ventricle) by the appearance, in the midst of the contractions of the type described above, of a prolonged pause in diastole. After an interval one or two more such pauses occur, and the intervals of regular contraction become shorter until the pauses become separated by a single beat. The rhythm is no longer regular, as the pauses vary very considerably in length. Sometimes each pause is followed by two contractions separated by a diastole of the usual length of the first stage. The excursion towards diastole is generally considerably greater than in the rest of the stage, and very much greater than in the normal heart. The degree of contraction is sometimes less than before the pauses began, but in other cases is more complete. Sometimes the length of the pause varies in alternate beats, and then the systole is less complete after the long pause than after the shorter. The period of activity of the heart seems practically of the same length as in the rest of this stage, but during the pause the heart continues to dilate for some time before coming to a complete standstill.

This phenomenon lasts for a variable time, sometimes extending over several minutes, at other times, where larger quantities were injected, being confined to a few beats. The rate then remaining unchanged, the excursion towards diastole generally shortens while that towards systole increases. Then each pause is followed by one or two rapid contractions, the number of pauses gradually become fewer and the intervals between them longer, and the heart passes into the second stage. I must remark that after this phase of excessive vagus activity the rhythm of the heart does not undergo the

gradual acceleration which is seen when this phase is absent, but passes at once to a very quick tempo, generally exceeding the normal rate, and possibly even that seen after paralyzing the inhibition by atropin.

This phase is by no means always, or even generally, present. I find it marked in about one-third of my tracings. It is evidently due to excessive inhibition and may therefore be accorded a place in the first stage of digitalis action. It is in fact merely an exaggeration of the features of the therapeutic action. On section of the vagi in the neck during it (see Exp. II), the rhythm at once returns to that of the rest of the first stage, which points to a stimulation of the centre in the medulla. It does not occur in atropinized dogs, and in fact only in animals in which the heart is in a practically normal condition and in which the inhibitory centre is in a state of undiminished or perhaps of exaggerated irritability. The most apparent explanation is that the stimulation of the centre increases until it culminates in this phenomenon. At the same time I have seen the ordinary slowing, caused by electrical stimulation of the vagus, suddenly pass into equally marked pauses without any increase in the strength of the current. This is, however, rare, and more frequently electrical stimulation causes fatigue of the vagus terminations, so that I am inclined to think that the drug as it accumulates in the medulla stimulates the centre more and more strongly until this phase sets in.

The changes seen in the ventricular muscle during strong stimulation of the vagi are, according to Roy and Adami, whose observations I can confirm from my own experience, slowing, irregularity in rhythm, with pauses in diastole, increased diastolic dilatation and less complete systole. The only difference during digitalis action is the increase in systole which is generally present. This is undoubtedly due to the muscular action of the poison, as in the rest of the first stage. In some cases, however, the inhibitory action is so strong as to conceal the increase in systole, so that the tracing may correspond completely to that obtained on stimulation of the vagi.

In the stage of recovery from this pause phase the decrease in diastole, the quickening and the increase in systole are probably due

partly to this muscular action overcoming the inhibition and partly to the fatigue of the latter.

The tracings hitherto described were taken from the left or right ventricle by means of the single myocardiograph. No difference could be detected in the tracings obtained from the two sides of the heart. I must emphasize this fact that no single feature can be found specifically indicating that the tracing was obtained from either ventricle, because Openchowski states that the right heart shows none of the symptoms of the action of this series. On the contrary, the right ventricle shows at least as evident modifications as the left, and I have therefore attached the myocardiograph rather more frequently to it, as it is much more accessible than the left. After it was proved that both sides of the heart showed symptoms of digitalis action, it was obviously necessary to find whether the time at which the changes in each occurred was the same, and I have therefore registered the movements of the two ventricles simultaneously in a number of experiments. Roy and Adami apparently attached two sliding needles to the same perpendicular rod in their myocardiograph. I could not satisfy myself that the movements of the one needle did not hamper those of the other, as the perpendicular rod is seen to move to a considerable extent in experiments where only one needle is used. I have therefore duplicated the apparatus throughout. Of late I have used a modification of the myocardiograph which is certainly more easily attached than the original and which gives better results, at any rate in my hands. It will be described in a later paper from this laboratory.

In the first stage the changes observed in the two ventricles resemble each other very closely. The rhythm is the same, and the slowing is due in each to prolongation of the diastolic pause mainly. The extent to which the excursion is changed in diastole and systole seems to vary somewhat in the two cavities, but this is probably accounted for by the difference in the length of the muscles which move the two levers. In some of my tracings the right ventricle seemed more affected than the left, while in others the reverse was observed. In general it may be said that *the two ventricles undergo simultaneous changes of the same kind and to the same degree in the first stage of digitalis action.*

AURICULAR MOVEMENTS IN THE FIRST STAGE.

Tracings were obtained generally, but not exclusively, from the right auricle, as it is much more accessible than the left and the apparatus can be attached to it with much less disturbance of the heart's position. The two auricles present, as far as I have observed, no important differences in their reaction to digitalis.

In some cases the tracing resembles exactly that from the ventricles. Slight slowing is accompanied by a greater shortening in systole, while the diastole may be slightly increased, remain unchanged, or become less complete than normally, these features being rather slowly developed and persisting until the second stage sets in. (See Plate XV, Fig. 3, *a* and *b*, which, however, is exceptional, in that there is no slowing of the heart, but a very marked increase in the excursion towards systole.)

In others the changes in the auricle are perfectly characteristic. The rhythm is slowed, the diastolic relaxation may be increased, unchanged, or diminished, but the contraction, instead of being more complete, as in the ventricles, becomes progressively smaller. The length of the excursion of the lever may rapidly be reduced to one-eighth or less of the original, and eventually its movements may be barely visible. This condition may persist for a long time, in fact almost to the end of the first stage, the auricle beating slowly and weakly, and evidently propelling only very small quantities of blood into the ventricle (Plate XVII, Fig. 5). This form of contraction is that occurring most frequently in the auricle, especially with strophanthin and digitalin. It is generally preceded for a short time by a stage of increased systolic contraction, but, when large quantities of the drug are rapidly injected, may come on immediately.

In the auricle also occurs a phase of extreme slowing in those experiments in which the "pause phase" sets in in the ventricle (Plate XVII, Fig. 5). I have observed it more frequently after erythrophlœin than after the others, but it is by no means rare after the injection of strophanthin. It is preceded by the form last described, and its onset is marked by occasional pauses in diastole corresponding to those seen in the ventricle at the same stage. When this phase is fully developed

the diastolic pauses are much prolonged, while the extent of contraction and dilatation remains the same as in the rest of the stage. A considerable degree of irregularity is, however, to be seen, not only in the length of the pause, but also in the length of the excursion of the lever, exactly as in the corresponding ventricular tracing. A very marked difference between the two tracings exists, however, as the auricular contractions never reach the normal, much less exceed it. Not infrequently the diastolic pause of the auricle exceeds ten seconds in length. The contraction following such a standstill is always much larger than the contractions seen in the rest of this phase.

A more extreme development of this form is complete stoppage of the auricle in diastole, which occurs in some experiments and lasts for a considerable time. It then regains its former slow rhythm with prolonged diastolic pauses, which still vary considerably in length and are followed by contractions of different force and extent. The rhythm slowly quickens, while the excursions increase in extent, and the second stage sets in, presenting features which will be described later.

Tracings taken on fast-running drums did not show in the auricle the prolongation of the time spent in full systole which was seen in the ventricle. In some contractions it seemed somewhat prolonged, but in others it remained unchanged. It can be said that in the auricle the prolongation of the full contraction is not by any means invariable, and in fact may be rather exceptional.

In the auricle the same forces are evidently at work as in the ventricle. In the first type described we have the muscular action developed very fully, as is shown by the greater degree of contraction attained and the varying dilatation in diastole. On the other hand the slowing and the occasional increase in diastole indicate the activity of the inhibitory mechanism. In the second form the same factors are active, but here the vagus action overcomes the muscular. It has been shown repeatedly that the changes produced by cardiac inhibition are much more marked in the auricle than in the ventricle, and it is only to be expected therefore that the muscular action of digitalis should here give way to the inhibitory. Besides, these two factors are

in much more direct opposition here than in the ventricle, for in the latter the vagus lessens the completeness of systole, it is true, but only by causing increased diastolic relaxation, and does not change the actual extent of contraction (Roy and Adami). In the auricle, on the other hand, the contraction is lessened by inhibition, the height to which the lever is raised in systole being considerably lower than normally. In order to improve the systolic contraction of the auricle to the same extent as it does that of the ventricle, digitalis would have to cause much more profound changes in the auricular muscle than it does in the ventricular, and of course the thin auricular wall allows it a much smaller field to work in. We find accordingly after digitalis in the auricle a tendency towards less complete systole instead of the more complete one of the ventricle. In the "pause phase" of the auricle the muscular action seems at first sight entirely absent. The slowing, the diminution in the force of the contraction, the prolongation of the diastolic pause and the occasional complete standstill must all be attributed to the inhibitory action. On the other hand the diminution in systole is not so great as would be produced by the same degree of inhibitory action unopposed. This was shown very clearly in experiments in which both auricle and ventricle were attached to recording levers. On stimulation of the vagus in the neck the rhythm of the ventricle was slowed and the auricular contraction diminished in size, and on somewhat stronger stimulation the auricle ceased altogether, while the ventricle continued beating at a slow (spontaneous) rhythm. After the injection of the drug the same slow ventricular rhythm was observed, but now the auricle was no longer in a position of diastolic standstill, but was beating, although slowly and weakly. In order to explain this it must be assumed that here too the muscle is directly affected by digitalis. And in the same way we must assume that during the standstill of the auricle the same muscular action is present, although here it is rendered entirely latent by the strong inhibition. If during the slow rhythm or standstill the vagi be cut, the auricle shows the same changes as the ventricle does ordinarily. *The muscular action of digitalis, then, extends to the auricle as well as to the ventricle, although in the former it is often concealed, owing to the in-*

hibitory mechanism having more influence on that division of the heart and there opposing it more directly than in the ventricle. The difference in the tracings of the first stage in the auricle and in the ventricle is to be attributed entirely to this more powerful inhibitory action.

SIMULTANEOUS TRACINGS OF THE AURICLE AND VENTRICLE IN THE FIRST STAGE.

In many experiments the right auricle and ventricle were attached to the double myocardiograph. The left auricle and ventricle were examined less frequently owing to the derangement of the normal position which is necessary for this purpose, but no difference could be found between their behavior and that of the right heart.

In tracings obtained in this way the two cavities preserve exactly the same rhythm as long as the pause phase does not set in in either one of them. Taking those cases first in which this does not occur, we find the ventricular contraction entirely independent of the auricular as far as force and completeness are concerned. The changes in the systole and diastole of the former are the same, as far as I have observed, whether the auricle is modified in the same way or whether it passes through its characteristic form of lessened contractions. The ventricular systole follows the auricular as in the normal, with this difference, that the auricular pause in systole seems sometimes to last throughout the ventricular contraction, while normally the auricle begins to dilate while blood is still leaving the ventricle (see the diagram given by Roy and Adami, *Practitioner*, xliv, p. 251). I have attempted to show this on fast drums, but have been unable to do so, as these cases in which the auricular systole is prolonged by members of this group are comparatively rare.

As soon as the pause phase sets in in either cavity, the rhythm of each becomes entirely independent of that of the other. These pauses may set in simultaneously, but I have several tracings which show the auricle in this condition, while the ventricle maintains its former rhythm for 20 to 30 seconds. The ventricle then sets up its spontaneous rhythm, which is generally slower than that of the auricle (Plate XVII, Fig. 5), and bears no relation to it whatever. I thought at first that it might be the half-rhythm described by Gaskell in the cold-

blooded heart, but am convinced that the connection between the two cavities is entirely ruptured. In half-rhythm the ventricular contraction is seen to follow every second beat of the auricle after the same pause as in the normal heart, but no such sequence could be made out here. The ventricular contraction is generally slower than the auricular, but by no means always so. During the long pauses of the auricle, rhythmic contraction goes on in the ventricle without the slightest interruption, and during the complete standstill of the former the same amount of blood is probably expelled from the ventricle as before.

The explanation of this difference of the rhythms may be the following: The inhibition of the heart normally stops the auricle completely and allows the latent spontaneous rhythm of the ventricle to make its appearance. In the pause phase of digitalis action the same inhibitory power is present, and the ventricle therefore assumes its usual activity. But the auricular muscle is thrown into a condition of increased irritability, and therefore continues to contract in spite of the vagus activity. The reason why its contractions do not set up a more rapid rhythm in the ventricle must be that the impulse is blocked between the auricle and ventricle, and Gaskell has shown that in the cold-blooded heart stimulation of the vagus actually tends to hinder impulses from passing through the heart muscle. In the dog the same probably holds true (McWilliam, Bayliss and Starling), the irritability of the auricle is sufficiently increased to cause contractions, but these are too weak and the barrier raised by the inhibitory activity is too strong to allow them to pass into the ventricle, which therefore keeps up its own rhythm unaffected by the condition of the auricle.

As the action on the auricular muscle becomes stronger and the inhibitory mechanism gets fatigued, the auricular contraction becomes more rapid and more complete, the ventricular still maintaining its former rhythm for some time and then generally rather suddenly adopting the rapid rate of the second stage. The auricle not infrequently remains considerably slowed long after the ventricle has reached its greatest rapidity, and in some cases never reaches an equal rhythm throughout the experiment. The complete independence of the rhythm is well shown in one of my tracings (Plate XXII, Fig. 20*a*)

in which the sudden change of the ventricular rhythm sets in during a long pause of the auricle. The auricle continues to contract with a slight acceleration, while the ventricle passes through the progressive acceleration of the second stage and eventually comes to a standstill before the auricle has reached its normal rhythm.

Experiment VI, April 6.—Small dog narcotized with morphine and acetone chloroform. The double myocardiograph was attached to the right auricle and ventricle.

Time.	Rate of ventricle in 10 seconds.	Distance of systole of vent. from abscissa. mm.	Distance of diastole of vent. from abscissa. mm.	Excursion of vent. lever. mm.	Rate of auricle.	Distance of auric. syst. from abscissa. mm.	Distance of auric. diast. from abscissa. mm.	Excursion of auric. lever. mm.
11.35	30	77	117½	40½	30	22	58	38
.36	2 mg. erythrophlœin hydrochlor. injected into the vena saphena.							
.37	26	75	117	42	26	35	58	23
.38	3 mg. erythrophlœin hydrochlor. injected.							
.39	22	71	118	47	22	47	54	7
.41	6	74–75	114	40–39	9	46–47	51	4–5
.44	6	85	127	42	11½	43–44	53½	10–9½
.47	3 mg. erythrophlœin hydrochlor.							
.47½	5½	90	130	40	2	32–34	59	27–25
.48½	34	91	130	39	7	43–47	54	7–11
.51½	35	87	132	45	10	37	57	20
.54	35	84	132	48	17	27–32	57–59	30–27
.55	34	84	130	46	24	27–22	58	31–36
.56	35	irregular groups of 2d stage.			30	irregular groups of 2d stage.		

In this experiment at first the rhythm of the auricle and that of the ventricle are equally slowed, and the ventricle continues to follow the auricle. At 11.41, however, the pause phase sets in in each and the rhythm becomes independent. At 48½ the second stage sets in, the ventricle suddenly becoming greatly accelerated owing to the muscular action. The injection which causes this acceleration in the ventricle only increases the inhibitory slowing of the auricle. Later the ventricular rhythm remains constant, while the auricle slowly accelerates until it eventually reaches its normal rhythm. In the ventricle the systole is at first somewhat improved, but during the pause phase it becomes much less perfect than before and fails to recover during the

acceleration. At first the diastolic dilatation is somewhat lessened, but it soon increases in the pause phase and continues markedly increased to the end. The auricular systole becomes less perfect as soon as the inhibition becomes marked, and fails to recover its normal extent up to the end of the experiment. The auricular diastole is less perfect during the "pause phase," but is less changed than any of the other positions. The excursion of the ventricular lever is not much altered in this experiment, in which erythrophlœin had even less action than usual in causing increased systole. It must be remarked, however, that an unchanged excursion of the lever may indicate a much larger output if the contraction begins from a widely dilated position of the heart, as it does in this experiment. The auricular excursion is less than the normal throughout, and as the diastolic dilatation is scarcely increased at all at any point of the tracing, the amount of blood driven into the ventricle by the auricular contraction is much diminished.

Experiment VII, March 19.—Large dog narcotized with morphine and acetone chloroform. Myocardiographs attached to the right ventricle and right auricle.

Time.	Rate of vent. in 10 secs.	Distance of syst. of ventricle from abscissa.	Distance of diastole of vent. from abscissa.	Excursion of lever of ventricle.	Rate of auricle in 10 seconds.	Distance of syst. of auricle from abscissa.	Distance of diast. of auricle from abscissa.	Excursion of lever of auricle.
3.18½	25	63	98	35	25	16	41	25
3.19	0.5 mg. strophanthin injected into the saphenous vein.							
3.21	25	50	93	43	25	10	41	31
3.22	24	50	91½	41½	24	8	42	34
3.24½	24	45	91	46	24	—½	41	41½
3.25½	24	40	96	56	24	0	42	42
3.26	Second stage set in.							

In this experiment the inhibitory mechanism is entirely inactive. There is, therefore, no slowing and the changes in the auricle are exactly the same as those in the ventricle. The diastolic dilatation is little changed in the auricle, is somewhat lessened in the ventricle. On the other hand the shortening in systole is very much greater after the injection in both divisions, and the excursion of the levers is of

course augmented accordingly. So far as the muscular action is concerned, then, the auricle undergoes the same changes as the ventricle.

CARDIOMETRIC TRACINGS IN THE FIRST STAGE OF DIGITALIS ACTION.

From what has been said regarding the changes in the contraction of the different heart cavities, it will be recognized that the cardiometric tracing shows considerable variations in different hearts and presents great difficulties in analysis. I may, therefore, be allowed to explain shortly what one may expect to find recorded in these tracings. The cardiometer then enables us to measure the total amount of blood in the heart at any moment, whether the blood be contained in the auricles or ventricles. On the other hand it is impossible to distinguish whether any accumulation of blood indicated by it is contained in the one ventricle or the other or in the auricles. The contraction of the auricle is not recorded at all, as no blood enters or leaves the heart thereby, and the total volume is therefore unchanged. The contraction of the ventricles, on the other hand, is indicated and the amount of blood leaving the ventricle is measured. This is the chief object of the cardiometric tracing—to measure the output of the ventricles per beat and per unit of time. On the degree of systole and diastole indicated by the lever I have laid less weight, because this does not necessarily indicate the amount of blood in the ventricles at these two periods, but the total amount in the heart. Thus although the ventricles were to empty themselves much more completely than normally the cardiometer might indicate a larger amount of blood in the heart than usual, owing to the auricles having failed to reach their normal contraction, and therefore containing more blood at the end of their systole and during that of the ventricle. In the same way an increase in the volume of the heart in diastole need not indicate dilatation of the ventricles, but stoppage of the auricle in diastolic distension.

In some cardiometric tracings from the cat's heart under members of the digitalis series, I found the systolic volume of the heart actually decreased, while in others it remained practically unchanged, and in others (more especially with erythrophlœin) a rapid increase in the total amount of blood contained in the heart at the end of the ventricular systole manifested itself. In the first set of observations the

increased completeness of the ventricular systole was evidently sufficient to compensate for the increase in the residual blood of the auricle, or possibly these may have been cases in which the muscular action was equally marked in the auricle and ventricle. In the last I have no doubt that the ventricular contraction was increased, but this was masked entirely by the increase in the residual auricular blood.

The height reached by the lever during the diastole of the ventricle was uniformly increased, partly no doubt owing to the increased ventricular dilatation, but also possibly to dilatation of the auricle.

The "contraction volume" or output of the ventricles per beat is uniformly much increased whether slowing of the rhythm is marked or not. This is of course due to the increased systole, aided in some cases by an increased dilatation of the ventricles.

In regard to *the amount expelled per unit of time,* my results *varied a good deal according to the extent to which slowing of the rhythm occurred.* In those cases in which the change in the rhythm was but slight the blood expelled in ten seconds was distinctly augmented, while in other experiments in which more marked slowing occurred, the output, although at first increased while the retardation was slight, became later practically normal, and still later, when extreme slowing set in, sank below the normal.

The increase in the output may be very considerable, amounting in some cases to 50 per cent, and between this and a decrease in the output every gradation may be met with, as the opposing influences, the slowing and the increased contraction volume, compensate each other.

Experiment VIII, February 14.—Large cat narcotized with morphine and acetone chloroform. Curara. Cardiometer attached to the heart and a mercury manometer connected with the left carotid.

	Rate in 10 seconds.	Contraction volume.	Percentage increase in contraction volume.	Output in 10 seconds.	Percentage increase in output in 10 seconds.	Blood pressure in millimetres of mercury.
Before erythrophlœin	36	18½		666		22
After erythrophlœin	33	24	30	792	19	30–33
Later	28	28½	54	798	20	35½–37

In this experiment the contraction volume is markedly increased, while the output in ten seconds is much less altered, although it also rises. The compensation for the increase in the contraction volume is well seen in the last observation, where, although the amount expelled by the heart in each contraction is increased by 24 per cent, the total output for ten seconds is altered less than one per cent. As my experiments were not performed for the purpose of finding the absolute output, but merely to compare the amount of blood passing through the heart before and after the drug, I have not calibered the apparatus, and the numbers given denote the length of the lever excursion in millimetres. It is scarcely necessary to remark that the total output per unit of time is found by multiplying the contraction volume by the number of beats. Roy and Adami found the output considerably reduced by vagus stimulation, owing to the slowing which occurred. The muscular action after digitalis is, however, enough not only to compensate for this diminution, but to change the negative to a positive. The increase in the output per beat is also, of course, to a large extent due to the increased dilatation of the heart in diastole.

Experiment IX, March 7.—Cat narcotized with morphine and acetone chloroform. Atropin given in sufficient quantity to paralyze the vagus, as ascertained by electric stimulation.

	Rate in 10 seconds.	Contraction volume.	Percentage increase in contraction volume.	Output in 10 seconds.	Percentage increase in output per 10 secs.
Before strophanthin	18	23		414	
After strophanthin	18	27	17½	486	17½
Later	18	29	26	522	26
Still later	18	30½	33	549	33

Here, as no slowing occurred, the contraction volume and the output in ten seconds of course increase together. As the results of the cardiometer experiments in this stage, then, it may be stated that the work done by each contraction of the heart is markedly increased, while the work actually done by the heart in a given time may be

increased to a much smaller extent, may remain unchanged, or may be diminished according as the rhythm is much slowed or not.

MYOCARDIOGRAPHIC TRACINGS FROM THE VENTRICLES IN THE SECOND, IRREGULAR, OR PERIODIC STAGE.

During the second stage of the action of this series on the ventricles the inhibitory action slowly lessens and eventually disappears altogether, the rhythm rising to the normal, or more frequently above it. As the acceleration progresses, the contractions generally become very irregular, not so much in rhythm as in the degree of systole and diastole which they attain. In these irregularities a distinct periodicity may be observed, and I have therefore called this the periodic stage. The tracings obtained now vary exceedingly in different hearts, and even in the same heart at very short intervals. They may, however, be classed into several types, and these I shall describe, premising that several types may, and in fact generally do, occur in the same heart, and that between the different types many intermediate forms occur.

In the first type (Plate XIX, Figs. 7 and 8) the contractions form well-marked groups of very characteristic appearance. Thus commencing with a very small contraction, imperfect in both systole and diastole, the succeeding beats increase in size in both directions by a regular "staircase" until they attain an immense size, and then decrease by a corresponding staircase until the minimum beat is again reached, from which a fresh group begins. At first the number of contractions in each group is very considerable, but these soon become fewer and the staircase becomes steeper. The difference in dilatation between the large and small beats is not by any means generally the same as that in contraction. Sometimes the systoles remain practically unchanged, while the line of the diastolic excursions shows very marked waves. In other cases the systolic contraction alone shows the staircase, while the diastole remains practically unchanged, but in the great majority of the tracings both show large undulations.

Sometimes after this grouping has persisted some time, the type undergoes a modification, in that a group of large diastoles is, as at first, followed by a series of less perfect ones, but the systoles, instead of being more complete during the large diastoles, are more extensive

during the imperfect ones, so that the heart assumes alternately a position more towards diastole and one more towards systole. The change from one position to the other is marked by one or more beats which are imperfect in each direction. Not infrequently the two forms of grouping are present together in a more or less confused form (Plate XIX, Fig. 7), so that while in one group excessive diastole is accompanied by an increased systole, in the next the systoles corresponding to the largest diastoles may be very imperfect.

It might be supposed that this phase of the digitalis action was merely a prolongation of the first stage, in which the beats become periodically reduced to the normal size. This is, however, not the case, for the imperfect beats are generally smaller than the beats of the first stage, and even than those of the normal heart, while the larger contractions generally far exceed both in systole and diastole those of the therapeutic stage. The variation in the excursion of the lever is sometimes very great indeed. In Plate XIX, Fig. 8, the contraction varies from 35 to 70 mm., but in other tracings I have found even a larger relative variation, *e. g.* from 15 to 90 mm. In other cases the variation is comparatively small, amounting only to $\frac{1}{5}$–$\frac{1}{10}$ of the size of the larger excursions. As the groups become shorter, the variation in the size of the individual contractions generally becomes greater, the smallest becoming even more of a jerk and the larger extending further in each direction.

The rhythm of the heart is generally unaffected, exactly as many contractions per second occurring during the smaller as during the larger contractions. In rare cases, however (Plate XVI, Fig. 4, *d* and *e*), one finds among the large excursions a prolonged diastolic pause exactly corresponding to those in the pause phase of the first stage and evidently due, like them, to inhibitory action. When this occurs it reduces the number of the larger movements per second, so that the heart seems at first sight to beat more slowly than during the smaller contractions. If, however, this pause be discounted it is found that here too the rhythm is the same in each phase.

The rhythm of the heart during this type is generally somewhat slower than normal, but is quicker than in the first stage, this type

frequently occurring as the first symptom of the quickening of the beat seen in the later parts of the tracing.

The groups are at first of considerable length, frequently containing 20–30 contractions, but they soon become shorter. Sometimes it seems that a group of large beats becomes divided into halves, a depression occurring at the top of the diastolic wave and deepening in succeeding groups until there are two waves of equal length instead of one. More frequently the very long periods are entirely absent, comparatively short groups of five to ten contractions following directly on the first stage. In these shorter groups the alternations of excessive diastolic and excessive systolic movements are more frequently observed.

This type of regular "staircase" periodic variations may last for a considerable time or may form the prelude to another type which often follows directly on the first stage, especially when large quantities of the drug have been injected at one time. This form (Plate XIX, Fig. 9, and Plate XVIII, Fig. 10) shows much less regularity than the one just described, and without the experience of the latter there might be difficulty in recognizing the periodic character. It seems, however, merely a further development of the "staircase" groups, and in some hearts the intermediate steps may be traced very clearly. The groups here, however, contain much fewer contractions, and those which appear seem to represent the extremes of the first type, so that there are alternately two or three immense excursions in each direction followed by one or two very small ones imperfect both in systole and diastole. The staircase character is almost entirely lost, the contractions between those two extremes having disappeared. In addition to this the size of the large excursions and the degree of contraction and relaxation reached by them vary considerably, and in their turn the small beats differ also in point of size. As the first type changes to this form the large excursions become even more exaggerated and the smaller ones less perfect. In fact the large excursions in this type denote the largest movements of the heart in the whole tracing. Not infrequently after this type has persisted a longer or shorter time the heart suddenly ceases midway between systole and diastole of the smaller beats, and dilatation and delirium cordis close the experiment.

A further development of this type is where the group is reduced to two or three contractions (Plate XX, Fig. 16, *a* and *b*), an excursion which may extend to a fairly large diastole and systole being followed by a smaller one which is perfect in neither direction and may in extreme cases be merely an undulation on the line denoting the larger movement. The position of the heart during this "missed beat" varies. In many cases there occurs after a full systole a very slight relaxation followed by a return to systole, in others the heart dilates to a position midway between systole and diastole and then contracts imperfectly and relaxes to full diastole, while in a few cases where the heart had been exposed for a long time an almost complete relaxation was interrupted by a short contraction. At other times the line denoting contraction of the heart was interrupted. After a normal contraction and dilatation a fresh contraction would commence and be carried out to a varying extent, only to be interrupted by a very slight relaxation, which was followed by a full systole. All of these forms may occur in the same heart, in fact may follow one another in the course of a few seconds. The size of the missed beat is no more constant than its position. It is often merely a slight undulation on the tracing, and from this one may see within a short time every variation in size up to a full beat. In some cases the increase in size of the missed beat forms a regularly progressive series. The contractions between the missed beats are rarely equal in size and in the extent of relaxation and contraction which they attain (Plate XX, Fig. 16), more generally showing extreme variation, one beat reaching far beyond the average in both directions and the next being of only moderate extent. The average position of the heart also varies considerably. Sometimes the most extreme diastole never reaches even that seen before the injection of the digitalis, and the systole is more complete than at any other part of the tracing. This occurs especially when a large quantity is injected, the first stage is short and this type sets in soon after. When the vagus stage had lasted long, and especially if large quantities of the narcotic had been given, the tendency to increased systole seemed to disappear and the heart moved further towards the diastole position than in the first stage. When this type

of missed beat sets in, the heart is invariably accelerated. Not only has the inhibitory action entirely disappeared, but the rhythm is considerably more rapid than before the injection of the drug. Even when the inhibitory mechanism had been previously paralyzed by atropine the heart was still further accelerated during this and the following types.

In another type (Plate XX, Fig. 15), instead of one missed beat there may be two or three or more intervening between two full beats, and the tracing may assume the form of a series of comparatively small undulations interrupted here and there by an excursion towards diastole and systole. The position of this undulating line is generally near the line of full systole, but not infrequently midway between this and full diastole. If it is at full systole of course the excursion of the large contraction is merely a relaxation and a return to the line of undulation, while if it lies midway the excursion towards diastole is followed by another to systole, after which the lever-point returns to the level of the undulations again. After a time the intervals between the full beats become longer and longer, and these become less perfect, while the missed beats become smaller and eventually pass into delirium cordis, the heart dilating from the position of the last undulations to extreme diastole, where it remains quivering for many minutes.

In other cases, instead of a series of missed beats being interrupted by full beats at intervals, one finds a series of large beats interrupted by a short phase of missed ones, which are again followed by full beats (Plate XX, Fig. 13, and Plate XXII, Fig. 12). Then suddenly, instead of the full beats returning after the interruption, delirium cordis sets in. The failure of the heart in fact very often comes very suddenly. The contractions may be fairly regular and satisfactory excepting for the occasional occurrence of missed beats, when suddenly standstill occurs.

Rarely one finds the missed-beat type preceded by another form of periodicity which is also derived from the original type. I have mentioned that in this a series of large diastoles sometimes alternates with another of large systoles. If these are contracted down from groups

to single beats we have alternately an excursion from full diastole to imperfect systole, followed by one from imperfect diastole to full systole, and this form is met with, though it lasts but a short time, before one or other form passes into a "missed beat."

As a general rule the contraction of the heart muscle passes through several of these types, gradually becoming more irregular and less effectual until after a longer or shorter period of missed beats it passes into delirium. Sometimes, however, a heart whose contractions have been reduced to a hovering about the line of systole with occasional full beats shows signs of recovery. The full beats become more numerous, the missed beats fewer, and eventually the tracing comes to resemble one of the earlier types. A comparatively small dose again injected generally causes the return of the hovering, which then goes on to delirium. Curiously enough, in several experiments in which the extreme forms had been reached—missed beats occurring every third or fourth contraction and every beat differing from its neighbors in size and the extent of systole and diastole—a new injection, instead of increasing the disorder, caused a temporary improvement, the excursions increasing in size and becoming more regular and the missed beats disappearing. This was, however, soon followed by complete collapse. Stimulation of the vagus in one or two experiments was followed by the same result. Marmé and Popper note a similar improvement in the blood-pressure tracing from stimulation of the vagus and a repetition of the injection. This might lead one to suppose that the condition of extreme irregularity is due, at any rate in part, to exhaustion of the heart. That this is not the correct explanation, however, is shown by the fact that it occurs after large doses only a few minutes after the injection and after the heart has been exposed only a very short time, as well as by the fact noted above, that evident symptoms of recovery are often seen from the extreme conditions of irregularity. The real explanation is the renewal of the inhibitory action, as will be shown later, the stimulation of the vagus and the new injection both acting in the same way. When the inhibition is again overcome by further muscular action the irregularity returns in even more marked form and soon passes into delirium.

Occasionally the ventricular contraction improves before death, and may in fact become fairly regular. It then ceases suddenly and delirium sets in. This regularity was at first very puzzling. It is due to the stoppage of the auricle and the consequent cessation of the interference, as will be explained more fully later.

As a general rule the periodic variations set in very soon after the acceleration of the heart. Sometimes one or two minutes of fairly regular contractions followed on the first stage (Plate XXII, Fig. 20*a*), but more frequently the commencement of the second was marked by a great undulation in the systolic or diastolic line. In other tracings the ventricular contractions remain of almost uniform force for a long time (see Experiment VI), the rhythm becoming more and more accelerated, until at last the periods set in and standstill occurs a few minutes later (Plate XXII, Fig. 20, *a* and *b*). In two tracings I can find no distinct periods in the ventricular tracing. The contractions in these cases remained of the same character as at the beginning of the second stage until they terminated in delirium, the shortening in systole persisting throughout and a high blood pressure being recorded up to the moment of the ventricular standstill.

In a number of experiments, after the lever had ceased to move for several seconds, contractions recommenced quite suddenly, lasted for a few moments and again ceased. This was occasionally repeated several times and delirium cordis then set in, the heart dilating to a position far beyond anything seen during the tracing and quivering for several minutes before coming to rest. This temporary recovery of the heart muscle was seen much more frequently in the auricles than elsewhere, and it was repeated much more frequently in these than in the ventricles.

The ventricle ceases finally in a position generally midway between systole and diastole. The subsequent dilatation during the delirium is probably due to the paralysis of the muscle, not by the drug directly, but by the products of its own activity.

It must not be supposed that all of these types occur in every experiment. On the contrary, one sees a few of the types and intermediate forms in each heart. They are all developments from the original

large groups first described, and the evolution from one to another may be easily traced. The process seems to consist of a diminution of the smallest beats and an enlargement of the largest accompanied by a shortening of the length of the period. The change from one form to another is occasionally very abrupt, and, more especially when large quantities are injected, the most extreme forms may follow very closely on the first stage. In experiments in which the pause phase occurred in the first stage, it often passed directly into one of the more extreme types of irregularity, and the acceleration of the rhythm was much more rapid in its onset than in the other forms.

Tracings of the irregular stage taken on rapidly revolving drums added but little definite information. The irregularity is of course the same and the variations in different hearts are equally marked. In these tracings, however, it is seen more evidently that not only the size of consecutive beats varies very greatly, but also their whole form. Thus one beat shows a rounded and fairly long diastolic pause, while the next forms a very acute angle in diastole, the heart having scarcely completed its relaxation before a fresh contraction sets in. In others it is evident that dilatation was imperfect when the contraction recommenced. The systole is no more regular, the duration of the pause in full contraction being sometimes longer and sometimes shorter in consecutive beats, but the tracing rarely showing the sharp angle seen in diastole. There is, therefore, seldom a jerk contraction with immediate relaxation, but the heart has a distinct tendency to remain for some time in the contracted position. On the other hand the great variation in the extent of systole is rendered even more evident in these tracings than in those taken on the slow drum. In these also it is clearly seen that the failure of the missed beats to reach systole is not want of time, the heart frequently remaining contracted for some time at some distance from the maximum systolic line.*

The extreme diversity of the tracings in this second stage precludes the possibility of giving any general description that would include

* I reserve a more detailed description of the second stage as seen when registered on quick drums, for a future paper, in which the cause of the different forms will be discussed.

most of the features observed even in a single heart. The most characteristic feature is the periodicity, and I think the tracings appended show most of the forms observed. The first explanation of this feature that occurred to me—that it was due to the artificial respiration—was shown to be incorrect, because when this was suspended the periods were unchanged. The inhibitory mechanism is so prominent in the first stage that it might be supposed that it might play a part in eliciting the most characteristic feature of the second, but the periodic variation occurs quite as markedly after the injection of atropin.

The periodic tendency seems therefore entirely independent of the inhibitory apparatus, which, however, is generally more or less active during the beginning of its manifestation, as shown by the somewhat slowed rhythm as well as by the occasional appearance of a diastolic pause in the midst of a group noted earlier in this paper. None of the features seemed to point to the activity of the accelerator nerves, and I have neither stimulated nor divided them.

At the beginning of the second stage, when the periodic variation first makes its appearance, there is generally present an exaggerated excitability of the central nervous system which manifests itself in movement of various kinds. Thus although the supply of air to the lungs is maintained uniformly throughout the experiment, violent movements of the diaphragm and abdominal muscles are to be observed. These are perfectly rhythmical and are evidently due to stimulation of the respiratory areas. Other movements of a convulsive character are also present, resembling those seen under picrotoxin and other so-called "convulsive poisons." It seemed possible that these movements, by driving the blood out of the abdomen and muscles into the heart, might alter the character of the beat somewhat, although it would be difficult to explain thus the enormous variations seen. In the later part of the tracings, however, no such evidences of increased activity of the brain and cord are observed, while the periodic character may remain almost as marked as at first. Moreover, the periods set in in dogs whose movements have been rendered impossible by the previous administration of curara. This would therefore exclude the possibility of the periods having been caused by the muscular

movements. At the same time the spasmodic contraction of the arterioles from convulsive stimulation of the vasomotor centre is not excluded. The blood-pressure tracing (see Plate XIX, Fig. 8), however, shows only moderate undulations during this period, which are manifestly insufficient to cause the marked changes in the heart, but which are rather to be considered the effects of these changes. I think the periodicity, like the increased contraction of the heart during the first stage, must be attributed to a direct action of the drug injected on the heart. Knoll ascribes it to fatigue of the heart, but other substances, such as chloroform, which might be expected to have a more powerful action in this direction, do not cause this periodic phenomenon. In the frog's heart there are seen what may be called periodic variations at a certain stage of the intoxication with digitalis. One part of the ventricle remains contracted during several diastoles of the rest of the organ, and then dilates again while another part becomes contracted in the same way. Often a peristaltic movement may be made out, the blood being driven from one side of the ventricle to the other and back again by alternate contractions of the two halves. The myocardiograph records only the contractions of a single strip of muscle, and the question therefore arose whether the periodic character was not of exactly the same nature as the peristaltic movement of the cold-blooded heart and confined to the piece of muscle examined. On watching the heart, however, at this stage it is seen that the whole of a ventricle is concerned in the variation, and in the rabbit's heart more especially the change from large to small contractions may be made out very distinctly by the eye and finger. Another method of deciding this question which I have employed is the cardiometric. If the variation were confined to a small part of the heart one would scarcely expect a very marked change to be recorded by this instrument, while if the variations were equally marked in the cardiometric and myocardiographic tracings the inference would be that at any rate large parts of the heart, if not the whole of it, were affected by the change. As a matter of fact the cardiometer, as will be shown later, indicates that large divisions of the heart, sometimes even the whole heart, undergoes these periodic variations. Before giving the true

explanation of the irregularity, it will be necessary to discuss the changes seen in the auricle in the second stage, as these are closely connected with the ventricular periods.

SIMULTANEOUS TRACINGS OF THE MOVEMENTS OF THE TWO VENTRICLES DURING THE SECOND STAGE.

During this stage the rhythm of the ventricles remains the same. In none of my experiments in which the movements of both ventricles were recorded have I been able to find a single contraction of the one ventricle which was not accompanied by a corresponding movement of the other. On merely watching the ventricles it often appears that one beats more rapidly than the other. Even if the levers be observed, the same error is made, for the two writing points, instead of maintaining the parallel movements observed in the first stage, are seen at one time converging, at another time diverging, and then again running parallel. On examining the tracing, however (Plate XIX, Fig. 7, and Plate XXII, Fig. 12), it is found that the number of contractions recorded by each ventricle is exactly the same and that the illusion is due to one ventricle having made a very small contraction ("missed beat"), while the other performed a normal or even exaggerated excursion. I have paid the more attention to this point on account of the views put forward by Openchowski and Bayet. Knoll in his second paper also mentions the arhythmia of the different divisions of the heart, but may possibly refer only to the movements of the auricle and ventricle, and not to those of the ventricles. No such dissociation of the two ventricles as these authors assert is to be found in any of my tracings. This equality of rhythm is, however, the only feature in which the tracings of the two ventricles resemble each other in the second stage. The degree of movement in each individual contraction differs frequently in each division. Thus a missed beat in the right ventricle may correspond to an abnormally large one in the left, or the one tracing may show the most beautiful group periods while the other is contracting fairly uniformly (Plate XIX, Fig. 7). In general I have found the left ventricle maintain a fairly regular contraction longer than the right, but this rule is subject to numerous exceptions, and when the right reaches the more irregular forms no greater uni-

formity is seen in the left. Sometimes the two cavities seem to change in the inverse direction, the large beats of the right corresponding to the small ones of the left and *vice versa*. This, however, is purely casual, and a few moments later one may see the two levers carry out very large or very small excursions together. The tracings appended show better than any description can do, the remarkable divergence in the movements of these two divisions of the heart at this stage. The cessation of rhythmical movements in the two ventricles is subject to no less variation. In some cases standstill of the left precedes that of the right, although in my tracings the reverse sequence is the more frequent. The ventricles then occasionally recover for a few seconds, to pass ultimately into delirium cordis and extreme dilatation. The variation in the strength of contraction in the two ventricles can also be made out by direct observation, although the extent of the divergence is not appreciated until the graphic method has been adopted.

AURICULAR TRACINGS IN THE SECOND STAGE.

In the second stage the movements of the auricle present even less uniformity than those of the ventricle. When the slowing during the first stage has been moderate and the long diastolic pauses and accompanying arhythmia of the auricle and ventricle have not been developed, the auricular tracing resembles the ventricular in the beginning of the second stage, the same periodic changes and the same gradual acceleration of the rhythm occurring. After some time, however, the auricle suddenly ceases to beat in a position somewhat nearer diastole than systole, but not in full dilatation. This standstill is frequently final, the auricle giving no further signs of life, although the ventricles continue their contractions for some time. In other cases, however, the pause only lasts for a few seconds and the auricle recommences beating, sometimes at the same rate as before, but more frequently in a much accelerated rhythm and more irregularly (Plate XXI, Fig. 19*a*). After the lapse of some ten to thirty seconds it again comes to a standstill, and this alternation of feverishly hasty pulsations and of complete inactivity may be repeated a number of times before permanent stoppage of the auricle occurs (Plate XXI, Fig. 19*a*, *b*, *c*).

Sometimes the auricular movements gradually become smaller and smaller and eventually cease in diastole, from which they do not recover. In either case the auricle ceases here before the ventricle, but it does not dilate to its full extent nor pass into delirium cordis until the ventricle ceases. This is in accordance with the view that the extreme dilatation in which the whole heart is generally found after digitalis poisoning is not a direct effect of the poison, but of the inanition of the heart muscle, as the auricle is supplied with blood as long as the ventricle is in movement.

When extreme slowing of the heart rhythm has occurred in the first stage and the sequence of the auricular and ventricular rhythm has been lost, the auricular tracing in the second stage presents a very different appearance from that just described. Here the acceleration of the auricle is a comparatively slow process, while, as has been remarked above, the ventricle passes very rapidly from the stage of extreme slowing to that of marked acceleration. The auricular tracing still shows the characteristics of inhibition in the marked slowing as well as by frequent pauses in diastole (see Plate XVII, Fig. 5, and Plate XXII, Fig. 20). At the same time there is a gradual improvement in the contraction, the systole becoming much more complete. The auricle continues to accelerate its beat until it eventually attains the rapid rhythm of the ventricle, provided the latter continues its movements long enough. Until this occurs the excursions of the auricle remain fairly uniform, except that after a diastolic pause the systole frequently is larger than the one immediately preceding it. After the rhythm of the auricle has become accelerated so as to almost equal that of the ventricle, however, group periods may become developed and the usual irregularities of the second stage (Plate XXII, Fig. 20*b*). In those cases in which the acceleration of the auricular rhythm occurs later than that of the ventricle, the auricle frequently contracts as long as the ventricle, in some cases even longer, before passing into delirium.

The divergence of these two forms in the auricular tracing is evidently due to the different power of the inhibitory mechanism in different hearts and the varying degree to which it is stimulated by the

members of the group. As long as the inhibitory action is present to a very marked extent, the periodic phase, as will be shown later, cannot set in in either auricle or ventricle. When it is less fully developed, periodicity occurs in the ventricle and not in the auricle, and still later both divisions show equally marked periodic irregularities.

The pauses which occur in the auricular tracings first described are evidently not due to inhibitory action. They present none of the characteristic features and besides occur in atropinized hearts. I look upon them as extreme developments of the periods. At the same time I find it difficult to account for the alteration of the rhythm which follows them. The auricle may beat with perfectly regular rhythm before the pause and then resume its contractions accelerated to a rhythm more than half again as rapid as its former one.

SIMULTANEOUS TRACINGS OF THE VENTRICLE AND AURICLE IN THE SECOND STAGE.

As regards the character of the individual contractions, what has been said above as to the divergence of the contractions of the two ventricles may be repeated in regard to the auricle and ventricle. Even when the rhythm remains the same in the two divisions of the heart, there is no resemblance between the corresponding contractions. The character of the contraction in the one has no influence whatsoever on that of the other, a missed beat in the auricle being often followed by an abnormally large one of the ventricle and *vice versa*.

The rhythm of the auricle and ventricle remains the same, provided there has been no dissociation in the first stage, until late in the second stage. When, however, the auricle stops contracting, as it generally does, the ventricle continues without the slightest change in rhythm or force of contraction. When the auricle recommences again the two divisions no longer preserve their equal rhythm, the auricle contracting often nearly twice as fast as the ventricle. Here again the ventricle remains quite uninfluenced by the changes in the other division, undergoing a slight continuous acceleration whether the auricle is beating more rapidly or is in complete standstill (Plate XXI, Fig. 19 *a* and *b*).

If auriculo-ventricular arhythmia has set in in the first stage it continues during a variable time in the second. The ventricle assumes its rapid rhythm rather suddenly, while the auricle maintains the slow "pause phase" for a much longer time. The auricular rhythm then slowly quickens until it attains the ventricular acceleration, and then stoppage of the auricle may occur and its subsequent rhythm be much more rapid than the ventricular. As a general rule the auricle comes to a final standstill before the ventricle. When, however, the auricular slowing has been prolonged and the ventricle ceases before the auricle has reached an equal acceleration with it, that is when the auricle is still more or less controlled by the inhibitory mechanism when the ventricle fails, the former may continue contracting for several seconds longer.

In several experiments in which the auriculo-ventricular rhythm had attained a high acceleration, stimulation of the vagus in the neck was not followed by slowing of the heart, but the ventricle became more dilated in diastole and less shortened in systole, while the auricular contractions became much less strong. The inhibitory mechanism seems, therefore, still capable of causing its usual effects on the cardiac muscle, except that it is incapable of slowing the rhythm.

The independence of the four divisions of the heart as regards the nature of the contraction performed by each is therefore complete, in fact no better example of this could be found than in the second stage of the action of this series. The normal sequence of the auricle and ventricle is also interfered with by these drugs, while the association of the rhythm of the two ventricles, and probably of the two auricles, remains unimpaired.

The explanation of the whole of the phenomena of the second stage is, I think, to be found in the increasing irritability of the cardiac muscle, with or without the antagonistic inhibitory mechanism coming into play. Similar features occur in the later stages of poisoning with other drugs, such as aconitin, and I shall therefore not enter into the details of the subject here, but reserve them for a future communication and confine my remarks to what is absolutely necessary for the comprehension of the second stage of digitalis poisoning. The normal

heart must be considered to have two rhythms—the ventricular and the auricular—of which the former is generally entirely in abeyance, the ventricle receiving its rhythm from the auricle by muscular conduction. If, however, the auricular rhythm be obliterated, or the connection between the auricle and ventricle be cut off by crushing (Wooldridge) or by section (Tigerstedt) or by inhibitory influence (McWilliam, Bayliss and Starling), the ventricular rhythm sets in and the two cavities beat independently of each other as regards both rate and force.

Another way in which an independent ventricular rhythm may be set up is by stimulation of the ventricular muscle (Bayliss and Starling).

Two independent rhythms may occur in the heart, and the contractions of each of the divisions concerned may be perfectly regular in force, rate and size. This continues, however, only as long as the passage of impulses from the one to the other is blocked. As soon as two rhythms occur without any hindrance to their passage from one division to the other, the contractions of each become irregular, owing to the interference of the transmitted impulses with the contractions generated spontaneously in each division. An impulse may pass either to the ventricle from the auricle or in the reversed direction (McWilliam, Bayliss and Starling).

Returning now to the tracings obtained after digitalis, we find that in the first stage we often have the same rhythm in auricle and ventricle throughout. In this case the rhythm is auricular, the inhibitory action slowing it, but not being strong enough to block the impulse passing to the ventricle. As the action proceeds, the inhibition becomes weaker, or more probably the muscular action on the auricle overcomes the inhibitory and the rhythm becomes less slowed than immediately after the injection. The auricular rhythm is still, however, somewhat slower than normal owing to the inhibition. The muscular action is more marked on the ventricle and the inhibitory is less powerful. Accordingly we find the irritability of the ventricle at last so great that the slow auricular rhythm is no longer sufficient to satisfy it and the ventricle takes up its own rhythm, and is therefore

now set in motion by two sets of impulses, one generated in its own, the other derived from the auricular muscle. As long as the extraneous impulse reaches the ventricle during its refractory period it will have no effect, and if the two rhythms are nearly equal a number of impulses are therefore ineffective. In this way the irregularity becomes periodic, the periods being longer at first when the rhythms are nearly equal, but becoming shorter as they diverge more from each other.

In the auricle the condition is similar, the same interference of the two rhythms occurring and the same periodic irregularity. Occasionally, however, the auricle is fairly regular, while the ventricle is periodic. This is because the passage of impulses from the auricle to the ventricle is much easier than in the opposite direction. Thus we may have an interference occurring in the ventricle from the clashing of the auricular and ventricular rhythms while the ventricular impulses are unable to pass to the auricle, and the latter therefore beats perfectly regularly.

In case the inhibition is more complete, so that in the first stage the auriculo-ventricular rhythm is lost, the same process goes on. Here the ventricle accelerates but remains regular, because there is no interference in the rhythm, the auricular impulses being blocked at the junction of the two parts owing to the persistent strong inhibition (Plate XXII, Fig. 20*a*). The auricular muscle also becomes accelerated in course of time, and its impulses become stronger owing to the increasing muscular action. Eventually its impulses succeed in breaking through the barrier and the periodic phase at once sets in in both auricle and ventricle, or in the ventricle alone if the ventricular impulses are unable to pass in the reversed direction. When the two rhythms bear a certain relation to one another the result is complete standstill. This seems to occur more frequently in the auricle, or rather the standstill here is not attended by such fatal consequences as that of the ventricle. I have not yet been able to find precisely the conditions in which this standstill of the auricle occurs, but I have produced it repeatedly by stimulation of the unpoisoned heart, and have therefore no hesitation is ascribing the pauses in digitalis action

to the interference of two rhythms. When the auricle ceases to move the lever the ventricle not infrequently becomes regular again, but in other cases its irregularity is unchanged, because, as I believe, the auricle still continues to transmit impulses even when it no longer contracts itself.

I have mentioned already that a new injection of the poison or stimulation of the vagus not infrequently renders the ventricular contractions more regular. The action here is undoubtedly the inhibitory blocking of the impulses. This power of hindering the passage of impulses from the auricle to the ventricle remains long after the vagus has lost its power of slowing the rhythm, owing to the increased irritability of the muscle. Another way in which the action of the vagus in producing regularity might be explained is the weakening of the auricular contraction which it produces. This weakening of the auricle can be easily produced by vagus stimulation even in the last stages, but would scarcely explain the regularity of the auricle produced by the injection, although it may possibly also play a part in the action.

The periodic irregularity of the second stage is then due to the interference of two rhythms in the heart. This is not a purely hypothetical explanation, for almost all the irregularities which have been described above in the second stage can be produced in the unpoisoned heart by passing sufficiently rapid induction shocks through the different chambers. Some forms of irregularity I have not yet produced, probably owing to deficiencies in the apparatus at my disposal, but I think my tracings of artificial irregularity already justify me in explaining the digitalis irregularity in this way. The arhythmia and irregularity of the auricle and ventricle being thus disposed of, an explanation may seem required for the persistence of the common rhythm in the ventricles. It may be assumed that these have too much muscle in common to allow of the one contracting more rapidly than the other, but how then do they differ in the force of individual contractions? I have no experiments in which the two auricles are simultaneously recorded owing to the displacement of the heart which is necessary, and must acknowledge that the following explanation is

hypothetical, although I find no features in Knoll's tracings which refute it. My object in putting it forward is merely to show that the dissociation in force of the two ventricles is not incompatible with the view that I have suggested above. I assume then that the rhythm of the right auricle is the same as that of the left, as that of the right ventricle is identical with that of the left. The condition of the auriculo-ventricular connection is not, however, necessarily similar on the two sides. An impulse therefore passing from the right auricle to the ventricle may interfere with the contraction and inhibit it to the extent of causing a "missed beat." The same impulse passing from the left auricle to the ventricle is blocked on the way and the contraction of the left ventricle is therefore of ordinary force. In the same way the left auricle in this case would also be free from interference. The interventricular rhythm therefore is preserved owing to the large masses of muscle common to the two chambers. The interauricular rhythm presumably also lasts throughout from the same cause (see Knoll's tracings). The irregularity of the second stage is due to the interaction of each auricle and its corresponding ventricle, and if the bond between these be ruptured each will beat regularly though not necessarily in the same rhythm. If the bond be preserved and each has attained spontaneous rhythm, they will contract irregularly. If the bond be preserved on one side and ruptured on the other the one auricle and ventricle will beat irregularly, while the other auricle and ventricle will beat regularly. Thus suppose there exists an inhibitory block between the left auricle and ventricle while there is none on the right side. The two auricles contract rhythmically and the two ventricles. The right auricle and ventricle, however, interact on each other and their contractions show, therefore, periodic variations. The left ventricle can only communicate with the auricles through the right ventricle, and its contractions are therefore much less affected, or may scarcely be affected at all. As a general rule one finds that when one ventricle shows periodic variations the other also shows undulations to a very much smaller extent, and these may be due to this indirect communication.

After the periodic stage has lasted for some time, both ventricles

invariably show a practically equal degree of irregularity, owing to the impulses passing through from the auricles on both sides.

THE CARDIOMETRIC TRACING IN THE SECOND STAGE.

The cardiometric tracing shows the same modifications in the second stage as the myocardiographic. The same groups are met with in the beginning and the subsequent periods become equally irregular. The amount of blood expelled from the heart, the diastolic dilatation and the residual blood are found to correspond fairly satisfactorily with what has been inferred from the myocardiographic curves. The inefficiency of the smaller beats is shown even more clearly than by the other method, intervals of several seconds sometimes lapsing without any blood whatever leaving the heart, while during the periods of large contractions the output per beat far exceeds the normal (Plate XX, Fig. 17, and Plate XXI, Fig. 18). At a later stage alternate large and small contractions or other more or less irregular periodic forms are to be met with very much as in the tracings obtained from the muscle directly.

In many experiments the variations seen were considerably smaller than those generally obtained by the myocardiograph, and irregularities occur which have no counterpart in tracings taken with it. This is to be accounted for by the divergence in the contractions of the two ventricles described already. If one of these alternately empties itself completely and makes a missed beat, this will be recorded even although the other be contracting regularly, but the variations in the excursion of the cardiometer lever will not be so great as those of a myocardiograph attached to the periodic ventricle would be. In order to preserve a perfectly regular tracing in the periodic stage the contractions of the two ventricles would have to be completely complementary, that is the right must perform its shortest contraction at the same time as the left its longest, and the difference between the largest and smallest contractions of the one ventricle must be precisely equal to that of the other. Needless to say, this never happens, and accordingly the cardiometer tracing in the periodic stage resembles the myocardiographic in general features, although the variations are neces-

sarily smaller and additional irregularities occur from the clashing of the two ventricle contractions. Sometimes, however, one finds tracings which indicate that both ventricles are undergoing simultaneous periodic changes (Plate XX, Fig. 17). The auricles, as I have said, do not as a general rule cause any movement of the cardiometric lever. During the second stage, however, there generally occurs a sudden increase in the volume of the heart. This is, I think, the diastolic standstill of the auricle.

It is evident from what has been said that when the different divisions of the heart are not contracting in approximately the same way the cardiometer is of doubtful utility, and I have therefore paid less attention to its results in this stage than in the first stage.

THE BLOOD-PRESSURE TRACING.

In a good many experiments the blood pressure was recorded by means of the ordinary mercury manometer connected with the carotid artery, and in some of the tracings appended to this paper the blood-pressure curves are reproduced. So many observers have already analyzed the blood-pressure tracing under members of this series that I scarcely expect to find much new in it, and have rather attempted to show the condition of the heart corresponding to each known change of the tension.

In the first stage the increase in arterial tension not infrequently sets in before any material change in the heart occurs, although it never reaches any great height until the heart is also seen to be affected. In atropinized animals the rise in pressure is the only change seen in the carotid tracing (Plate XV, Fig. 2), but in ordinary cases the increase in tension is accompanied by marked slowing and enlargement of the pulse waves (Plate XV, Fig. 1, and Plate XVIII, Fig. 6). In these the increase in pressure is also somewhat less than when the inhibitory apparatus is paralyzed, and in fact when the pause stage sets in the pressure may fall considerably, sometimes reaching the normal or even below it (*cf.* Exp. V, and Plate XVI, Fig. 4). In experiments where these diastolic pauses set in very markedly the excursions of the mercury are enormously enlarged and frequently unequal in size.

The increase in the size of the pulse waves seems, therefore, due to the inhibitory action in one or other of its manifestations. In a number of cases in which the diastolic dilatation was absent or not well marked while the slowing was a prominent feature, the enlargement of the pulse waves was quite as great as in other cases in which both were equally well marked, while when the increase in diastole was more marked and the slowing was slight the large pulse waves were not met with (compare Plate XVI, Fig. 4, *b* and *c*). The increase in the size of the pulse waves, therefore, while possibly due in part to the increased amount of blood thrown into the arteries owing to the dilatation of the ventricle during diastole, must be mainly attributed to the slowed rhythm of the heart allowing the arteries to empty themselves more completely than normally during the interval between the contractions. The phenomenon is entirely independent of the increased completeness of the systolic contraction (compare Plate XV, Figs. 1 and 2), and the old explanation that it was due to increased strength of the heart must therefore be abandoned.

The results of the cardiometric tracings throw considerable light on the much-disputed question as to the cause of the increased blood pressure in the first stage. From these it is seen that the amount of blood thrown out by the heart per unit of time may vary very considerably under digitalis. Except, however, in cases where the slowing is very marked indeed, the output is increased, although this increase may be comparatively small, and seems insufficient to account for the marked rise in pressure. Thus in Experiment VIII the greatest increase in the output in 10 seconds was something under 20 per cent, while the blood pressure rose in the same time over 60 per cent. Now, the output is the only factor by which the heart can influence the mean blood-pressure tracing. Increased force of contraction can only possibly increase the size of the individual beats, the mean pressure remaining unchanged. In this experiment, however, the increase in the output falls short of the increase in the pressure by some 40 per cent, which must therefore be ascribed to some other agency than the heart, *i. e.*, to the peripheral vessels. Both factors are, therefore, to be considered as playing a part in the increased pressure. The im-

portance of the increased output is seen in those cases in which at one time marked slowing of the heart rendered its output temporarily less than normal, for the blood pressure fell sometimes to normal or even below it. At the same time the influence of the increase in peripheral resistance is shown in experiments in which with an unchanged output the pressure rose.

In the second stage the irregularity of the blood-pressure tracing is explained by the irregularity of the heart. During the stage of more prolonged periods the tension in the arteries remains high and shows periods of regular increase and decrease (Plate XIX, Fig. 8) resembling Traube's waves. As the irregularity progresses, however, the pressure begins to fall, and as soon as the missed beats occur they lead to a fall in pressure, which is not wholly compensated for by a subsequent series of large contractions, a certain degree of regularity in the heart's action being a *sine qua non* of a high blood pressure. A missed beat is generally accompanied by a sharp fall in pressure (see Plate XX, Figs. 13, 15 and 16), and if these occur regularly a wave effect may be produced somewhat resembling the respiratory waves. When an alternation of small and large contractions occurs the blood-pressure tracing may be very misleading, for one often finds a single pulsation produced by the large beat and uninterrupted by the smaller (Plate XX, Fig. 13). This single pulse is of course of considerable size for the same reason that the pulsations in the first stage are enlarged—the slowing. It not infrequently has a notch in its descending limb, or there may be two or more undulations on the descending limb and in the interval between the pulsations (Plate XX, Fig. 15). These secondary undulations are of course due to independent contractions of the heart of small size, but many authors have failed to recognize this fact and therefore describe occasional slowing in the second stage or just before death. When one considers that the two ventricles need not at all coincide in the strength of the contraction each performs, it is at once understood how the manometers in the pulmonary and carotid arteries need not agree in the number of pulsations per minute, the one marking large pulsations with or without dicrotic waves, the other smaller pulsations of double the rate. Openchowski's assertion of the

dissociation of the rhythms of the two sides of the heart was therefore natural, though incorrect. At the same time the danger of estimating even the speed of the irregular heart by means of the manometer is shown, and much more, that of deducing the condition of that organ from the blood-pressure tracing.

Another error that has been made in descriptions of the manometric tracings in the second stage is that the sudden descents of the needle indicate a stoppage of the heart in diastole, but from several of my tracings, as well as from a consideration of ordinary physical laws, it may be seen that stoppage in systole, or rather a series of small beats in systole or elsewhere, will have exactly the same effects as regards the blood-pressure tracing (Plate XX, Fig. 15). The fact that the rhythm seen in the blood-pressure tracing in the second stage is the independent ventricular and not a rhythm derived from the auricle as in the normal heart, explains how many observers could obtain no slowing of the pulsation in this stage by stimulation of the vagus. This absence of slowing does not indicate paralysis of the vagus ends, but excessive irritability of the ventricular muscle.

The discussion of the changes seen in the blood-pressure tracing during the whole of the second stage would occupy more time and space than is at my disposal, and the subject does not seem to me of great interest or importance. Suffice it to say that as the irregularities in the heart's contraction become more marked, the pressure gradually falls and eventually reaches zero, when the heart ceases. The fall in pressure is evidently due to the increasing inefficiency of the heart's action.

I have made no experiments on the pressure in the pulmonary artery and am therefore unable to state from my own observations the changes which occur in it. There is, however, a general consensus of opinion amongst those who have worked in this direction, that at any rate with strophanthin the pressure is little changed. In view of the fact that the right ventricle is affected in exactly the same way as the left by all of this series which I have examined, this seems to raise again the question whether the cardiac action of the series can raise the blood pressure or whether the unquestioned increase in aortic tension

is not due entirely to vascular changes. On the other hand the amount of blood expelled from the heart has been shown in a previous part of this paper to be distinctly increased, and the result of the cardiac action must therefore be to raise the blood pressure, at any rate to some extent. The only way of escape from this paradox is to assume that the pulmonary vessels are capable of allowing not only the ordinary output of the right ventricle to pass without resistance, but also to accommodate the larger amounts expelled after strophanthin, without enough resistance to increase appreciably the pressure in the pulmonary artery. The pulmonary vessels in fact have considerably less tone than the systemic and dilate much more readily under pressure from within. Digitalis apparently differs from strophanthin in the fact that the vascular action is much more marked not only in the systemic, but also in the pulmonary circulation, and a considerable rise of pressure is therefore found in the pulmonary artery after its injection.

SUMMARY.

In summing up the contents of the preceding pages it may be stated that the action of digitalis has been divided into two stages according to the changes evinced by the ventricles under its influence; of these the first is characterized by marked inhibitory action together with modification of the cardiac muscle, while in the second the inhibitory action is less marked and the muscular action becomes the more prominent feature.

The inhibitory action is due to direct stimulation by this series of the pneumogastric centrally in the medulla oblongata and peripherally in the heart. The extent to which the inhibitory mechanism is stimulated varies in different animals and with different members of the digitalis series. The muscular action of small quantities betrays itself in a tendency to increase the extent of the contraction, while in some cases the degree of relaxation reached in diastole is also lessened by it. In larger quantities the series increases the irritability of the cardiac muscle very considerably, and the spontaneous rhythm of the ventricles therefore becomes developed.

Through the interaction of these two factors in the first stage the

rhythm of the whole heart is slowed, the contraction of the ventricle is more complete, and the diastolic relaxation is generally increased, although it may be unchanged or lessened. The systolic pressure is increased and the fall from maximum to minimum pressure is slower than normal owing to the increased completeness and longer duration of systole (Rolleston). The auricles generally contract with less force and may relax more completely than normally. Sometimes, however, their contractions also are more complete than before the injection of the drug. This latter condition generally precedes the diminution of the force of the auricular contraction. This variation of the effects of digitalis in the auricle explains the changes in intra-auricular pressure noted by Kaufmann.

The contraction volume of the ventricles is always much increased, and the output per unit of time is generally augmented, and this together with the contraction of the peripheral arterioles causes an increase in the tension in the systemic circulation, an acceleration of the circulation, and possibly a temporary increase in the pressure in the great veins and in the auricle and ventricle in diastole (Kaufmann).

The pressure in the pulmonary artery is practically unaffected by some members of the series, while by others it is considerably increased. This difference in the reaction of the pulmonary circulation is due to the varying extent to which these drugs act on the peripheral arteries and not to any difference in their action on the two sides of the heart.

If the inhibitory action be very strongly marked the slowing of the heart may be extreme, the ventricles assuming their own spontaneous rhythm and all connection with the auricles being lost. While the contraction volume of the ventricle is still greater than normal, their output per unit of time may become less than normal, the aortic tension therefore fall and the rapidity of the circulation be lessened. The ventricles maintain their association throughout, and probably the rhythm of the two auricles also remains equal. The ventricular rhythm, however, becomes irregular owing to the variation in the duration of the diastolic pause. The auricles may cease altogether in diastole, or may continue to beat with a slower or faster rhythm than the ventricles.

During the second stage the rhythm of the heart becomes accelerated owing to the increased irritability of the heart muscle. The ventricle tends to assume a rapid spontaneous rhythm, while the auricular rhythm is also quicker than in the first stage. When these two rhythms interfere by the passage of impulses across the auriculo-ventricular boundary in either direction, irregularity of the heart is produced, generally bearing a distinctly periodic character. The ventricles continue to maintain their common rhythm, while the auricles and ventricles may contract at quite different rates. The two ventricles, however, do not necessarily contract with equal force, and the contractions of one may present periodic variations in strength, while those of the other may be almost perfectly uniform. The contractions of the auricles vary in the same way as regards each other and the ventricles. The inhibitory nerves are no longer able to slow the ventricular rhythm, but may affect the completeness of systole and diastole in the ordinary way. The auricular contractions can still be lessened in force and possibly be abolished by their stimulation, and the impulses passing between the auricle and ventricle may therefore be blocked and regularity of the heart produced by powerful inhibition. The irregularity of the contractions is therefore due indirectly to the increased irritability of the cardiac muscle and the acceleration must be attributed to the same cause. An extreme phase of this stage produced by the interference of the rhythms is a temporary standstill of one of the chambers, generally the auricle.

The irregularity leads to a lessened efficiency of the work of the heart. The output varies extremely in successive observations and the contraction volume of every individual beat may differ. The various chambers often show a tendency to dilate during this stage. The blood pressure in the systemic arteries at first remains high, in fact may be higher than in the first stage owing to the increased rapidity of the heart rhythm, but afterwards falls continuously as the periodic variations become shorter in duration.

The auricles generally cease contracting before the ventricles, but not invariably. There is no fixed order in the cessation of the ventricles or auricles. Each division comes to a standstill in a position

somewhat nearer diastole than systole and then passes into delirium and dilates to the fullest extent.

THE BEARING OF THE EXPERIMENTAL RESULTS ON THERAPEUTICS.

Finally some attempt must be made to correlate these changes in the heart with the therapeutic results attained by the use of this series. A number of theories have been put forward to explain the action of digitalis in heart disease. Traube's first view was that the slowing was the main factor, and undoubtedly this may have a beneficial effect in cases of tachycardia, although other drugs, such as aconite, which do not possess the characteristic muscular action, might be used in its stead for this purpose. The increased arterial pressure has also been considered of great importance in these cases, but cannot be considered the essential feature of the digitalis action, for an equal increase in pressure may be obtained by the use of strychnine and other drugs which, however useful in circulatory abnormalities, cannot replace digitalis. The diuretic properties of the latter seem due to the increased tension in the renal arteries, for Bradford and Philipps found that strophanthin, which constricts the arterioles less, causes also less diuresis or none at all in the normal animal. The rise in blood pressure must also play some part in therapeutics by improving the nutrition of the tissues, and especially of the heart itself, by a more rapid circulation. This greater rapidity of the circulation is, however, not due to the peripheral action of the drug, but to its action on the heart. In fact the peripheral action may in many cases be dispensed with to the advantage of the patient, as is shown by the success attending the combination of digitalis and nitroglycerine, the latter of which can only act in these cases by opposing the action of digitalis on the peripheral vessels. The rapidity of the circulation is of course increased whenever the output of the heart is augmented, but the acceleration may be much diminished by a contraction of the peripheral arterioles. The action of nitroglycerin in causing a return to their normal calibre would therefore be indirectly to increase the rapidity of the circulation.

The beneficial results of digitalis in quickening the circulation are therefore due in the main to its direct cardiac action, and the question

arises whether the changes described in the first part of this paper are sufficient to explain the therapeutic results or whether some other change must be sought for? And it must be noted that the features to be discussed are those of the first stage and indeed of the first part of the first stage, for the extreme slowing which I have described as the pause phase is not elicited in the therapeutic use of these drugs. And first of all in ordinary dilatation of the ventricle from any cause the action of digitalis is easily explained. In dilatation we find that the heart is not only unduly widened in diastole, but also that the amount of blood remaining in it in systole is greatly increased—the systole is rendered very much less complete than normal. The action of digitalis in increasing the contraction is therefore practically specific in those cases. In such a condition of abnormal dilatation in diastole it may be questioned whether digitalis through its inhibitory action will increase the diastolic distension. From my experiments I am inclined to think that in dilated hearts the muscular action overcomes the inhibitory in this point and actually lessens the dilatation. At the same time the dilatation produced by excessive quantities of acetone-chloroform may not be amenable to the same treatment as that seen in valvular disease, etc., and I shall therefore state it as a probability only that the diastolic dilatation in dilated hearts is not increased by digitalis, but may remain unchanged or even be lessened by it.

One of the results of dilatation is regurgitation through the mitral valve owing to the expansion of the ring surrounding the base of the valve. An increased contraction of the ventricle during systole will tend to contract this ring more and therefore lessen the regurgitation. Roy and Adami have shown that the papillary muscles contract with greater force under these drugs, and this will also tend to render the valve action more competent.

A tempting theory is that the auricular contraction is rendered more complete and prolonged as is the ventricular, and that the regurgitating blood, instead of striking on the relaxing wall of the auricle, is opposed by the completely contracted chamber, that in fact the closed auricle takes the place of the mitral valve. In my experiments, however, an actual increase in the contraction of the auricle

was of but short duration, and the diminution of the force of contraction was much more commonly observed. This action may conceivably occur, however, at any rate in some cases. It must be remembered that injection of the drug directly into the blood may not be followed by exactly the same order of events as its administration by the stomach, and it is quite conceivable that the slower absorption by this method may lead to the development of the muscular as opposed to the inhibitory action to such a degree that the auricular contraction is actually increased in force instead of being decreased. If the muscular action could be divorced from the inhibitory, or rather if a drug be found in which the inhibitory action is minimal, this effect on the auricle would certainly be present, for when the inhibition is paralyzed by atropin it occurs regularly. Unfortunately this action of atropin cannot be made use of in practical therapeutics. The question arises whether the addition of such a drug as spartein to digitalis might not by depressing the vagus be beneficial, in some cases at any rate, although spartein has little direct action on the heart muscle.

It may be questioned whether the prolongation of the ventricular systole is beneficial or not. In aortic regurgitation it may conceivably retard somewhat the return of the blood from the aorta, but here again the more complete emptying of the ventricle is more probably the important factor. The prolongation of the diastolic pause is undoubtedly a drawback here, although not such a serious one as Corrigan taught, for Roy and Sherrington have shown that the blood supply of the brain is actually increased by digitalis. Still, here again a drug with the cardiac action of digitalis and without its inhibitory action would presumably be of greater benefit. Stenosis of the orifices is also benefited probably by the improvement of the dilatation, but this stenosis is almost always accompanied by incompetency of the valves. In the right heart the therapeutic action may be explained in the same way as in the left. The increased contraction of the ventricle, and perhaps of the auricle, compensates here as on the left side for the dilatation and the valvular incompetency, whether these are direct results of disease of the left heart or of the lungs. In this relation it is noteworthy that digitalis increases the resistance to the passage

of the blood through the lungs to a very much greater extent than strophanthus, and it might therefore be expected that in such cases as dilatation of the right heart from emphysema, the latter would have more beneficial results than the former. I am unaware of any systematic examination of this point having been made as yet. The weakness of the heart met with in pneumonia may be in part due to the increased difficulty of the circulation through the solidified lung, but here, as in other fevers, is probably due rather to the toxic products absorbed and to the high fever. The action of digitalis here is therefore probably due to its improving the nutrition of the heart by increasing its output and the rapidity of the circulation, and not to any special action on the right side.

My experiments with each individual member of the series have been too few to draw conclusions as to the comparative value of each. In one only—erythrophlœin—have I found any very marked divergence from the general action, and this divergence is in the direction of a more marked inhibitory action and a less developed action on the cardiac muscle. In order to produce any important change in the latter, quantities of the drug have to be given, which call forth the most marked slowing and often arhythmia, and this fact seems to me sufficient to preclude the use of this drug in therapeutics, at any rate as a substitute for digitalis. As I have mentioned above, in order to advance further in the therapeutics of this group we must find drugs with a more decided cardiac action and a relatively smaller action on the inhibitory apparatus, while erythrophlœin tends in the opposite direction.

In conclusion I must express my indebtedness to Dr. Miller and Dr. Matthews, the assistants in the laboratory, and to Mr. Perkins and Mr. Wallace for the patient and valuable assistance they have given me in the experiments carried out in the course of this research.

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* This makes no claim to be a complete list of the papers on this series, nor even of those consulted in the course of this research. I think, however, that in it will be found most of the papers which have added appreciably to our knowledge of the pharmacological action of this series. A very large number of authors have contented themselves by showing that some new member of the series conforms to what was known at the time of the digitalis action, and these papers I have not included in this list, although I have perused most of them in the hope of gaining some new light on the subject.

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DESCRIPTION OF PLATES XV–XXII.

The tracings all run from left to right. The time-signal marks seconds, unless where specially noted. In all cases the downward movement occurs in systole; the upward in diastole.

Fig. 1.—Myocardiogram from the right ventricle and blood pressure from the carotid artery. *a*, normal; *b*, after strophanthin.

Fig. 2.—Myocardiogram from the right ventricle and blood pressure from the carotid after atropin. *a*, before strophanthin; *b*, after strophanthin.

Fig. 3.—Myocardiogram from the right ventricle (above) and the right auricle (below). *a*, before digitalin; *b*, after digitalin. There is no slowing nor any other symptom of vagus action in this tracing, although atropin had not been injected and the nerves were intact.

Fig. 4.—Myocardiogram from the left ventricle and blood pressure from the carotid. *a*, normal; *b*, *c*, *d*, *e*, after erythrophlœin hydrochlorate.

Fig. 5.—Myocardiograms from the right ventricle (above) and right auricle (below). Strophanthin in large quantity had been injected before this section of the tracing; complete arhythmia of the ventricle and auricle.

Fig. 6.—Myocardiogram from the left ventricle on a faster drum. Time marker is set for ⅕ second.. *a*, before strophanthin; *b* and *c*, after injection.

Fig. 7.—Myocardiograms from the two ventricles in the second stage. Right ventricle (upper tracing) shows very marked periodic variations. (Strophanthin.)

Fig. 8.—Myocardiogram from the right ventricle in the second stage. Blood-pressure tracing below. (Strophanthin.)

Fig. 9.—Myocardiograms from the right ventricle (upper) and right auricle (lower) in the irregular stage after digitalin.

Fig. 10.—Myocardiogram from the left ventricle in the irregular stage of strophanthin poisoning.

Fig. 11.—Myocardiogram from the right ventricle in the irregular stage of strophanthin.

Fig. 12.—Myocardiograms from the right ventricle (upper) and left ventricle (lower) in the second stage (antiarin).

Fig. 13.—Myocardiogram from the right ventricle and blood-pressure tracing from the carotid in the second stage. (Strophanthin.)

Fig. 14.—Myocardiogram from the left ventricle in the second stage after strophanthin.

Fig. 15, *a*, *b*.—Myocardiogram of the left ventricle and blood pressure at intervals of 5 minutes in the irregular stage.

Fig. 16, *a*, *b*.—Successive phases of the left ventricle during the second stage. (Strophanthin.)

Figs. 17 and 18.—Cardiometer tracings of the cat's heart in the second stage of strophanthin poisoning.

Fig. 19, *a*, *b* and *c*.—Myocardiograms of the right auricle (lower) and ventricle in the second stage of poisoning (strophanthin). In *a* the auricle ceases for several seconds, but recommences. In *b* and *c* the intervals of auricular inactivity are longer and the movements are smaller and fewer, and soon after *c* the auricles ceased altogether.

Fig. 20, *a* and *b*.—Myocardiograms from the right auricle (lower) and ventricle. In *a* the pause phase passes suddenly into the accelerated stage in the ventricle, the auricle still maintaining its slow rhythm. The accelerated ventricle is quite regular after a few seconds. In *b* the auricle beat is accelerated and stronger, and both tracings show beginning periods.

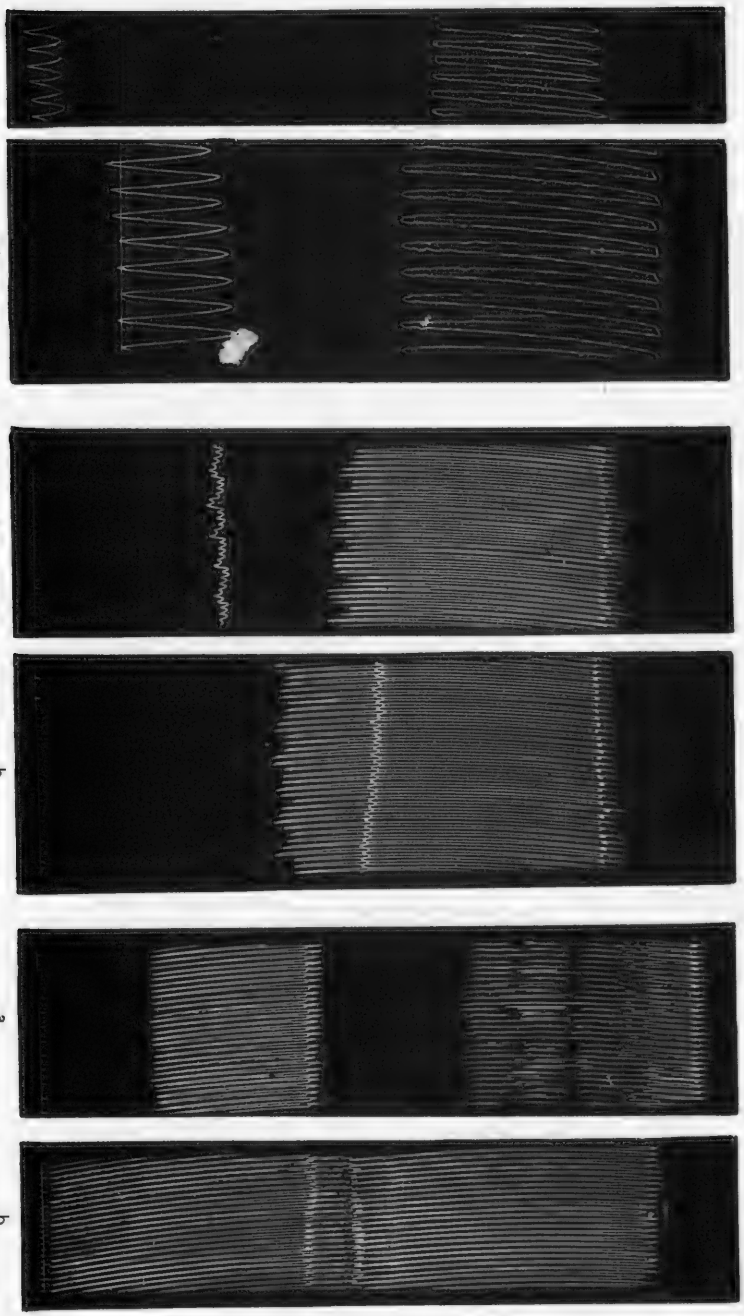


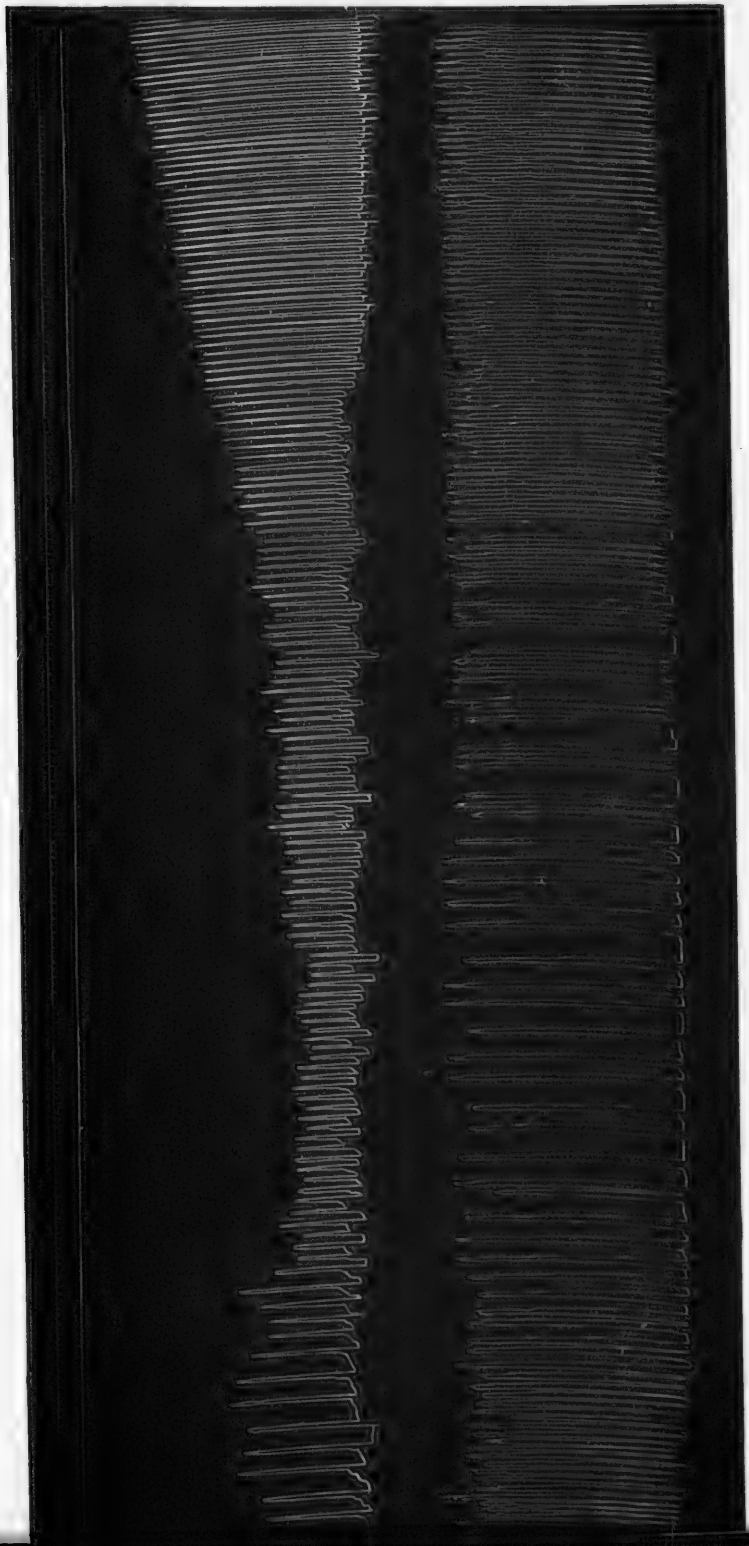
FIG. 1.

FIG. 2.

FIG. 3.

FIG. 4.

FIG. 11.



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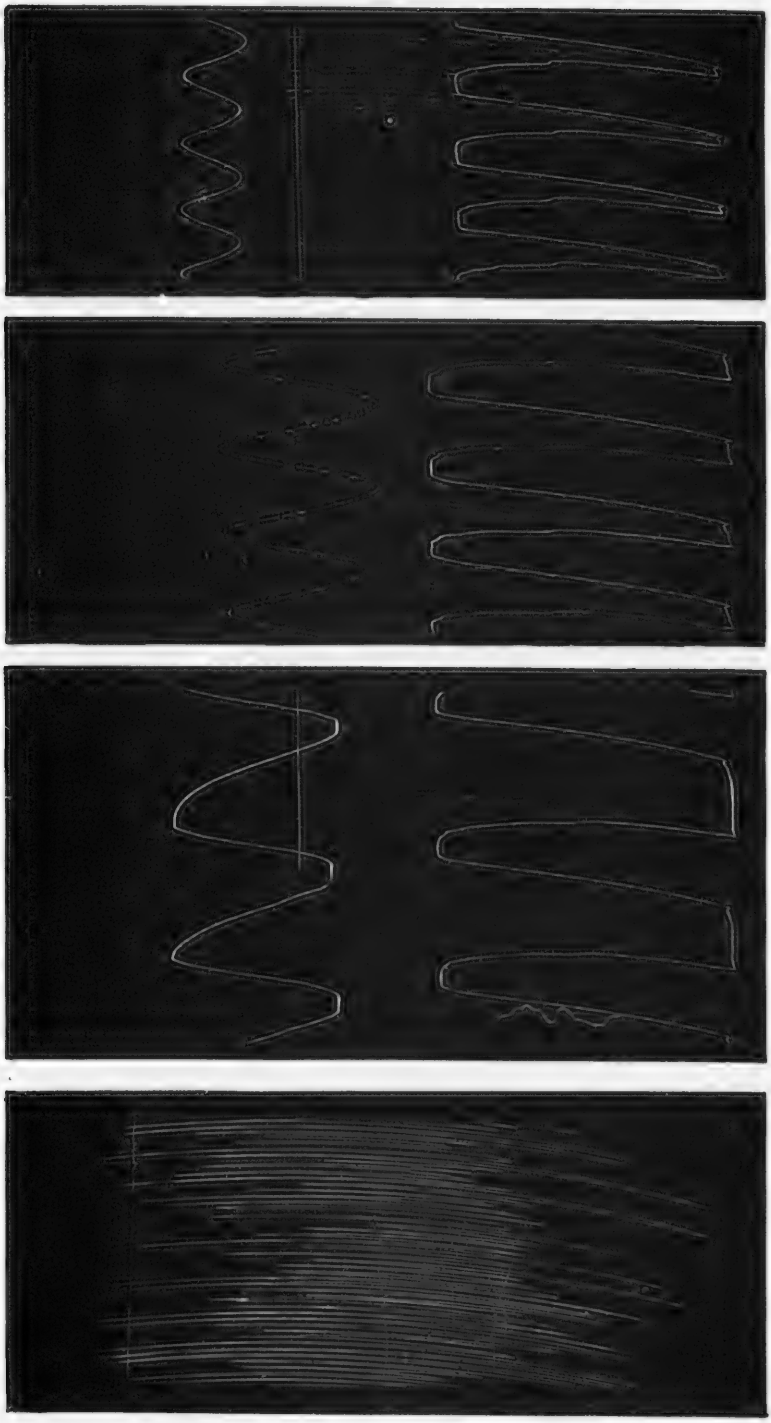
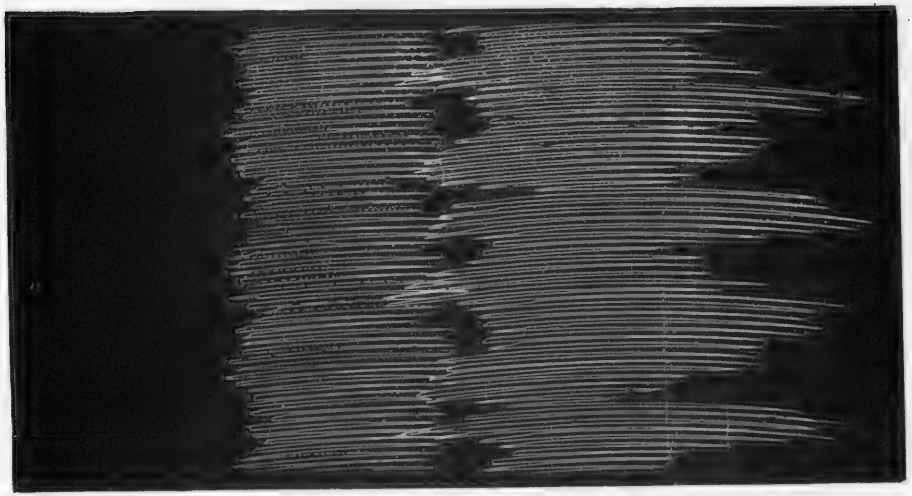


FIG. 6.

FIG. 10.



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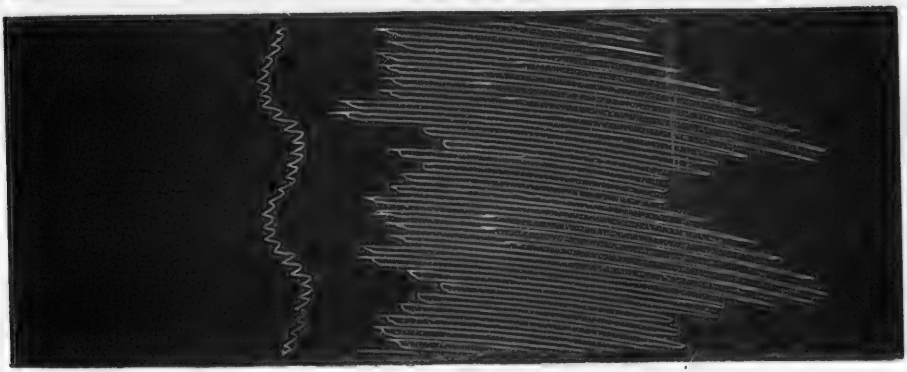

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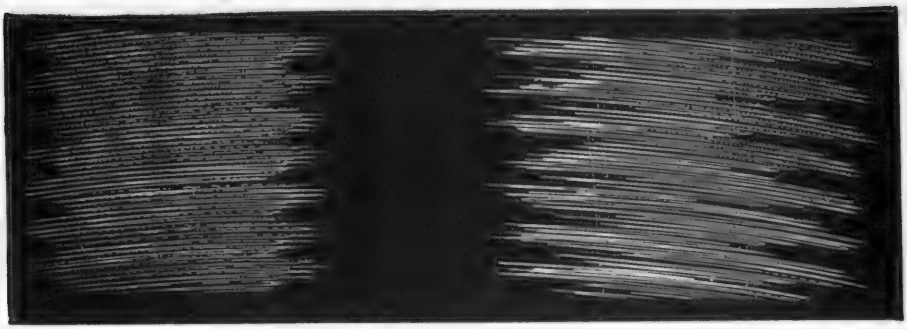

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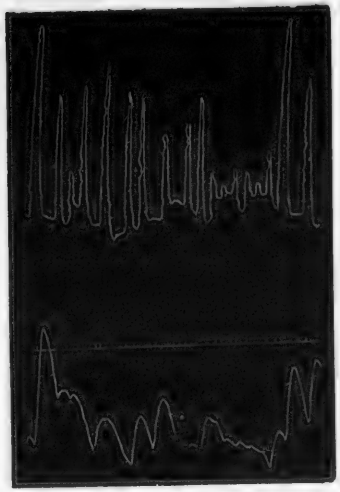
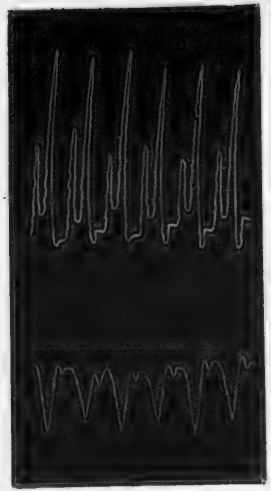


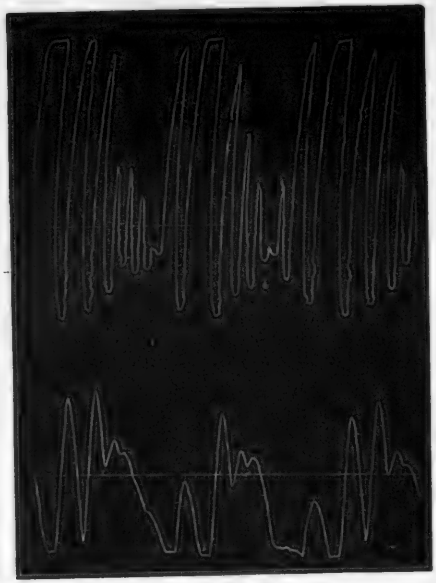
a



b

FIG. 15.

FIG. 14.



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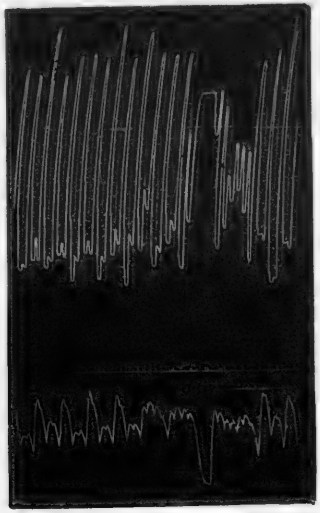

a

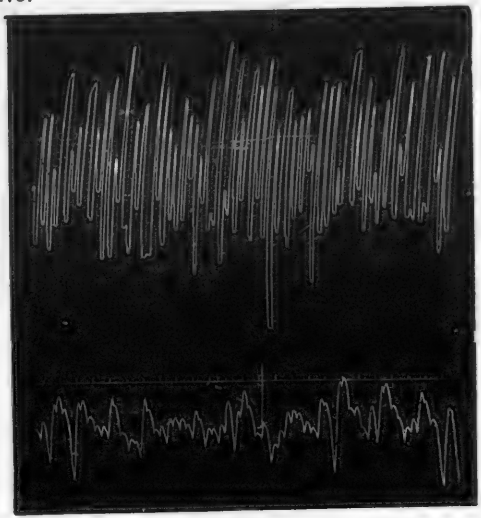

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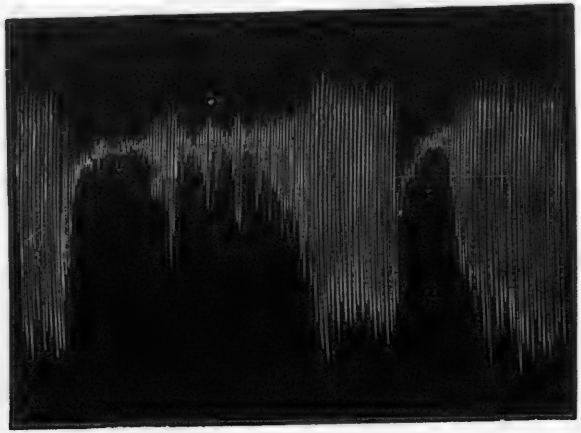
FIG. 16.



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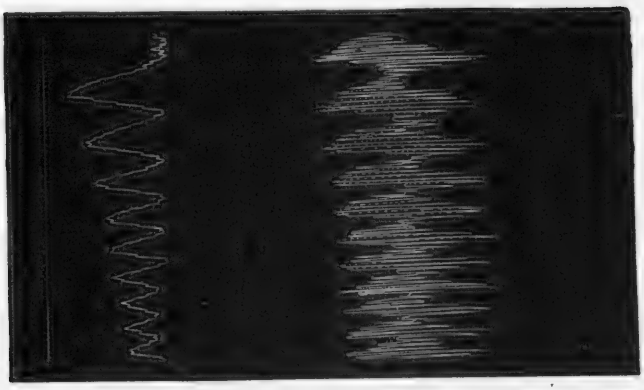

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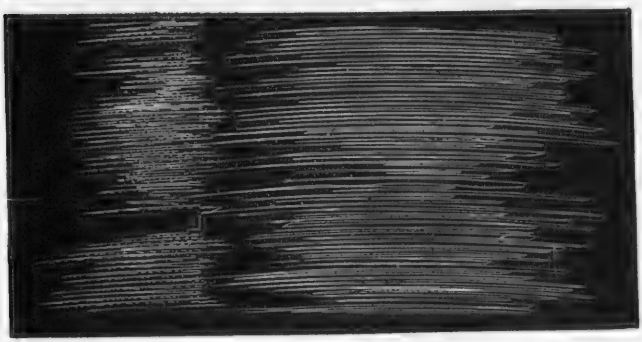


FIG. 19. a

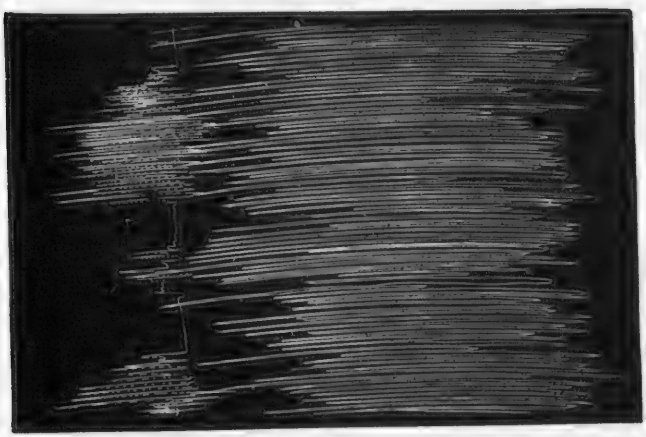


FIG. 19. b

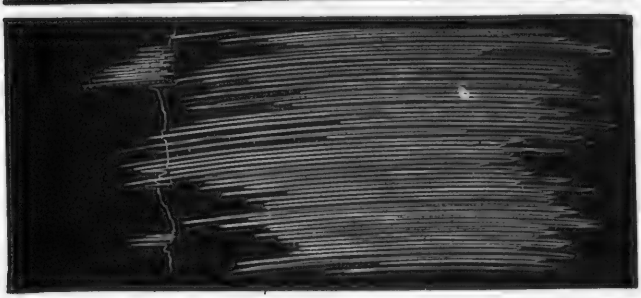


FIG. 19. c

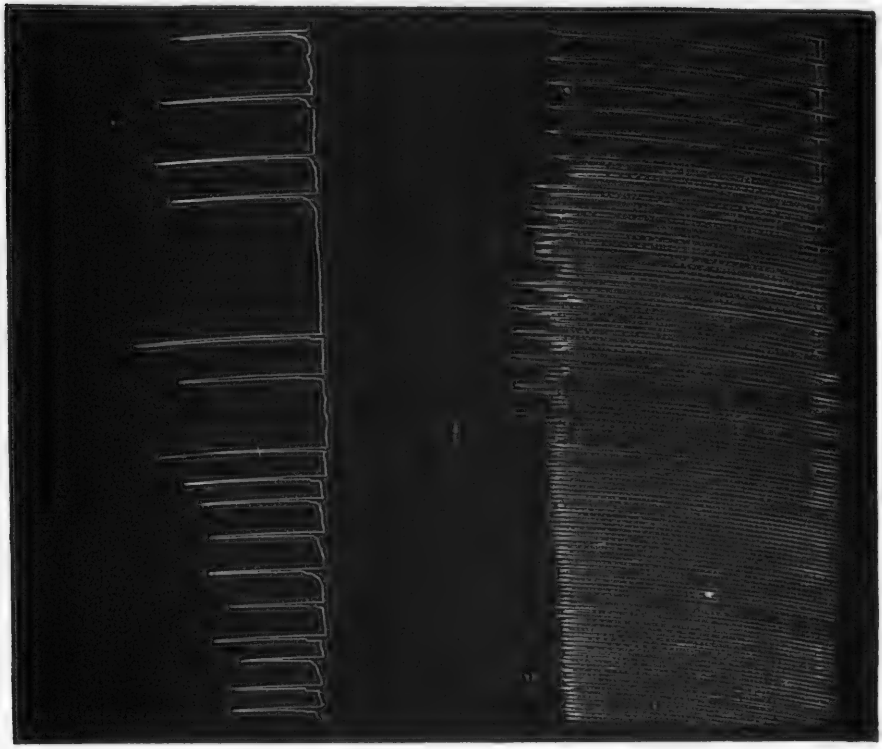


Fig. 20. a

Fig. 20. b

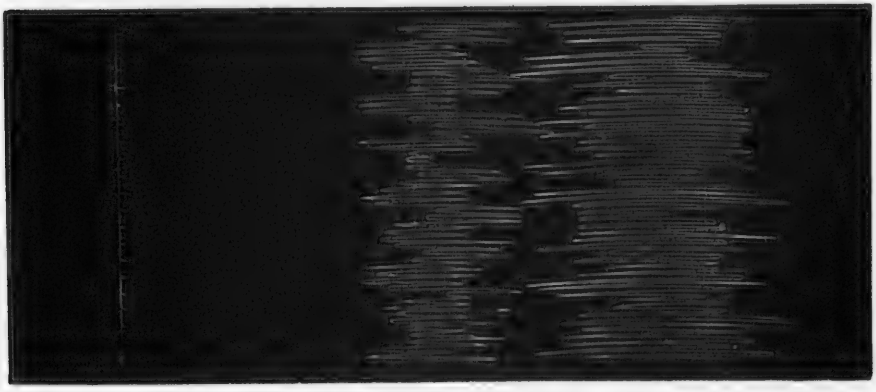


Fig. 12.

A GRAPHIC STUDY OF TREMOR.*

By AUGUSTUS A. ESHNER, M. D., Professor of Clinical Medicine in the Philadelphia Polyclinic; Visiting Physician to the Philadelphia Hospital.

(*From the Orthopedic Hospital and Infirmary for Nervous Diseases, Philadelphia.*)

Plates XXIII–XXX.

The work embodied in this report was undertaken at the suggestion of Dr. S. Weir Mitchell, whose hearty co-operation and material aid it further had throughout. Among the objects of the investigation was the determination (1) whether or not a demonstrable tremor exists in healthy individuals; (2) whether or not any relation or gradation exists among various kinds of tremor; and (3) whether or not various forms of disease present, as to their tremor, distinguishing characteristics.

The subject of tremor has always attracted considerable attention, especially in a clinical way, and a number of interesting graphic studies have been made. Most of these observations, however, have dealt only with the tremor associated with diseased states, particularly with regard to the form and frequency of movement and the influence of rest and action, or passivity and activity. With the exception of Peterson,† no one has, so far as I am aware, undertaken an analysis of the character of the movements, and it was hoped that this object might be fulfilled in the present study; but our efforts in this direction have not been entirely successful.

The first difficulty encountered consisted in the lack of a suitable apparatus, as none of those previously described appeared sufficient or available for the purposes of the investigation. A number of investigators (Debove and Boudet,‡ Maric,§ Horsley and Schaefer,|| Dutil,¶

* Read before the College of Physicians of Philadelphia, November 5, 1896.

† *Journal of Nervous and Mental Diseases*, February, 1889; *New York Medical Journal*, Oct. 11, 1890, p. 393.

‡ *Arch. de Neurologie*, i, 191, 1880–1.

§ Thèse de Paris, 1883.

|| *Journal of Physiology*, 1886, pp. 96, 111.

¶ Thèse de Paris, 1891.

Fernet* and Filliatre†) have used two tambours, connected by tubing which transmits to the second the movement imparted to the first. Others‡ have substituted a rubber ball for the first tambour. Still others§ used various forms of sphygmographs. Von Kries‖ preferred a steel spring to which a glass style was attached. Ughetti¶ employed an apparatus resembling the scales of commerce. This consisted of a vertical arm connected with a horizontal arm carrying a stylus. The vertical arm was supported by two springs and was provided with a toothed dial, on the face of which a needle registered the amount of pressure employed. The elaborate apparatus employed by Warner** permitted only the enumeration of various kinds of movements of the hand and its component parts. It consisted of (1) a series of rubber tubes to be attached to the hand, one tube to each finger or moving part; these were connected, by means of pieces of thin conducting tubing, with a set of tambours; (2) a frame supporting the recording tambours and electric signals; (3) an electric contact-making tambour, a modification of the Marey tambour, adapted to the purpose of actuating, and (4) an electric counter.

On looking over the ground, the conclusion was reached that the most suitable, as well as the most simple, apparatus would be one based upon the principles governing the construction of instruments already in use for the graphic study of various physiological phenomena, *e. g.* the pulse beat, the heart beat or the respiratory movements. The accompanying illustration (p. 303) and description represent the instrument devised for the purposes of this study and which is to all intents and objects nothing more than an inverted sphygmograph upon a large scale. It consists of a tripod (*A*) about four inches high, mounted upon a base of iron (*a*), to give it stability,

* Des Tremblements. Thèse de Paris, 1892.

† *Arch. de Neurologie*, September, 1894, p. 161.

‡ Marie, loc. cit.; Wolfenden and Williams, *British Med. Journal*, May 19. 1888.

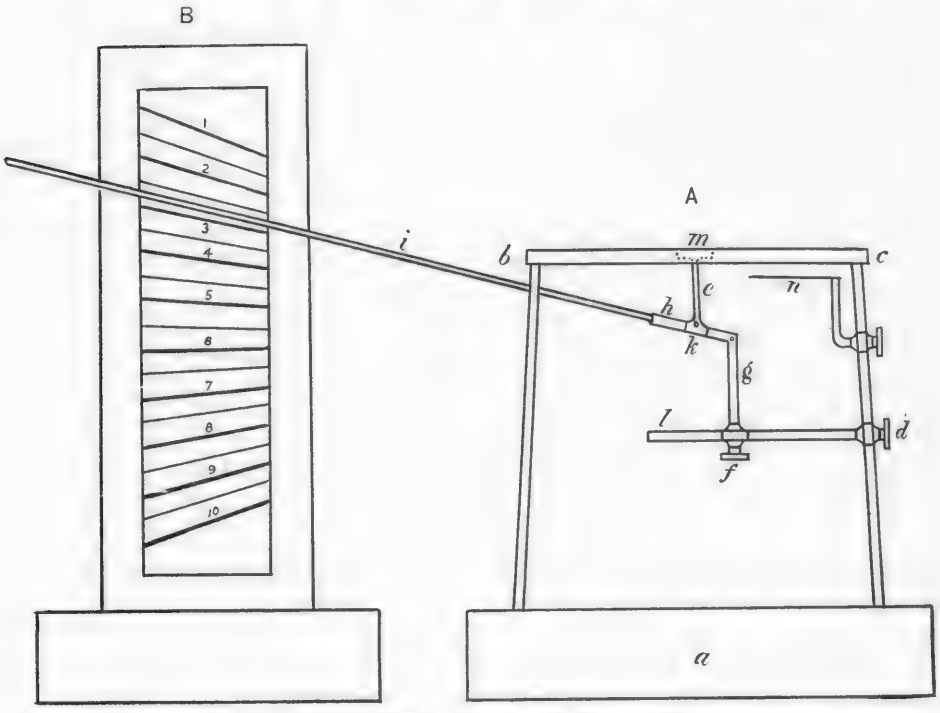
§ Grashey, *Arch. f. Psychiatrie*, xvi, p. 857, 1885; Huber, Virchow's *Archiv*, cviii, p. 45; Peterson, *Journal of Nervous and Mental Diseases*, February, 1889, p. 99; Dana, *Medical News*, December 17, 1892.

‖ *Arch. f. Physiologie*, 1886.

¶ *Rivista sperimentale di freniatria*, xix, fasc. 2, 3; *Rev. Internat. de Bibliogr. Méd., Pharm. et Vetér.*, 1893, No. 24, p. 451.

** *Journal of Physiology*, iv, p. 160.

and surmounted by a metallic ring (*bc*) four inches in diameter, over which is stretched an elastic membrane. Attached to one of the legs of the tripod, by means of a sliding ring and clamp-screw (*d*), is a horizontal metal bar (*l*) about two and one-half inches long, which can be raised or depressed. This rod in turn carries, also by means of a sliding ring and clamp-screw (*f*), a short vertical rod (*g*) an inch in length, which can be slid forward and backward. The upper



Tremograph and Pressure Scale. Diagrammatic, one-half actual size.

extremity of this vertical rod is bifurcated for the reception of a light bar (*h*), so pivoted upon either branch as to be capable of movement at its free extremity in a vertical plane, and with which the inscribing or registering needle (*i*) is connected through the intermediation of a prolongation of aluminum. Attached to this bar by means of a sliding band (*k*) is a slender rod (*e*) an inch long, jointed below to the sliding band and above to a small flat button (*m*), about $\frac{3}{8}$ of an inch in

diameter, which is glued to the under surface of the elastic diaphragm.*

It will be seen that every movement imparted, for instance by the fingers, to the elastic membrane will be transmitted to the registering needle, and in magnified degree, in inverse proportion to the length of the proximal arm of the lever formed by the arrangement of the constituent parts of the instrument. By this means it has been possible to demonstrate movements that would have escaped detection and record by the apparatus ordinarily employed. On the other hand, the sensitiveness of the instrument precluded its use in cases in which the movements were wide in range or wildly incoordinate. Under these conditions resort was had to the tambours in ordinary use (Plate XXIII, Fig. 2), which permitted, further, of simultaneous observations of the two sides of the body or of two or more different parts. The new apparatus, while possessing advantages over those previously in use, is not entirely free from objection. With it, as with others, it is difficult, if at all possible, to make the conditions always exactly alike. Thus the tension of the elastic membrane is variable under differing conditions; while the co-operation of the patient is required, both mentally and physically. Besides, in an investigation like this it is difficult to eliminate extraneous influences, such as are related to rest and activity, sleep, the emotions, hunger, the taking of food, stimulants, tobacco, etc.

In the endeavor to obtain as nearly as possible some basis of comparison, an attempt was made to fix the amount of pressure that should be exercised in placing the tremulous part, usually the fingers, upon the elastic diaphragm. This was successfully accomplished by the use of a scale constituted of lines radiating from a centre, which corresponded to the fulcrum of the lever contained within the instrument (*B*, p. 303). This was mounted by the side of the needle, and as a given weight was placed upon the diaphragm of the apparatus, the level to which the needle descended was noted, and for the individual observation represented a known amount of pressure.

*For the construction of the instrument I am indebted to Mr. F. F. Metzger, of Philadelphia. The photographs of the apparatus were kindly made by my friend, Dr. H. P. Boyer.

To distinguish our apparatus we have designated it a " tremograph," and the tracings secured with its aid, " tremograms."

The experiments were ordinarily conducted by having the subject place the fingers, especially the index, middle and ring fingers, upon the diaphragm and exercise a measured amount of pressure, one, two, three or four ounces, as the case might be. By means of a plate (*n*, p. 303), fastened beneath the membrane to one of the legs of the tripod, it was possible to have the subject approximate the fingers, above with the thumb, below in a prehensile attitude, without, however, bringing them in contact, and again with a measured amount of pressure. This attitude is not incomparable with that assumed, for instance, by the watchmaker in the execution of fine movements or by the surgeon in the performance of delicate operations.

In using the tambours, one of these (the transmitter) either was placed upon the lap of the subject, with the fingers gently applied, or was held between the partially flexed fingers and thumb, while the other (the receiver), through the intermediation of the style, was brought in relation with the smoked paper mounted upon the revolving kymographic apparatus.

In the course of this study upward of 1100 individual observations were made on more than 100 different persons. Nearly all of the subjects were derived from the Infirmary for Nervous Diseases—physicians, surgeons, nurses, patients—the last almost exclusively from the large clinical service of the Infirmary, generously placed at my disposal by the attending physicians, Drs. S. Weir Mitchell, Wharton Sinkler and Morris J. Lewis. A number of cases came from the private practice of Dr. Mitchell, and several professional colleagues kindly volunteered their services for the study of the tremor of the healthy. Watchmakers were studied through the courtesy of Messrs. Bailey, Banks and Biddle; and a number of men from the Old Men's Home afforded material for the study of the tremor of the aged.

While the results reached are not entirely satisfactory, in consequence partly of the inherent difficulties of the investigation and partly of mechanical deficiencies, they have still developed a number of interesting facts.

It was definitely determined that a tremor could be demonstrated

in healthy persons. This was to have been expected, as every muscular movement is made up of a series of alternate contractions and relaxations, occurring ordinarily with such frequency as to escape detection with the unaided eye.* As the frequency of contraction and relaxation diminishes, the tremor increases. The occurrence of tremor in healthy persons is further supported by the testimony of other observers.†

In a general way it was found that the frequency of movement bore an inverse relation to its extent, that is, the wider the range, the smaller the number of movements. This observation is of the utmost significance, as it largely negatives the likelihood of distinctiveness for the tremor of any disease, the extent of movement under any circumstances being extremely variable and influenced by various temporal conditions. Corroboration of this attitude is found in the statement of Fernet,‡ that the more frequent the muscular contraction occurring spontaneously or induced electrically, the less pronounced the tremor. Further confirmation of this position is found in the statement of Huber,§ that the rate of contraction varies in different muscles of the same individual, and in the same muscles on different days. Gowers|| also found considerable variations in the movements of different parts of the body of the same individual. Peterson¶ observed in cases of paralysis agitans that the movements were fewer in number as they were coarser, and that the rate of vibration differed in different parts of the body, and in the same part on different days.

Those acts were performed with the least tremulousness which the subject was mostly in the habit of executing (see Tracings 1, 2, 3, 4,

* If any one have doubts upon this subject, let him attempt to hold steadily in his hand a glass of water or other fluid and view the surface. In this connection I am reminded of an incident related of a skilled surgeon, noted especially for his steadiness of hand, who when spoken to upon the subject by a junior colleague was unwilling to admit that his hand shook. On placing, however, the fingers in a vessel of water, the rippling disturbance of its surface at once proved the contention of the younger man. If a photographic reproduction of the waves of motion generated under these conditions could be made, it might prove serviceable in such a study as has here been undertaken.

† Debove and Boudet, loc. cit.; Horsley and Schaefer, loc. cit.; Beaunis, quoted by Wolfenden and Williams, loc. cit.

‡ Loc. cit.

§ Loc. cit.

|| Gowers, Diseases of the Nervous System, 1888, p. 1000.

¶ Peterson, *New York Med. Journal*, October 11, 1890, p. 393.

Plates XXIV–XXVII). Thus the watchmaker, the laryngologist and the eye surgeon displayed less movement in the exercise of less pressure than in that of more, while those unaccustomed to delicate manipulations displayed more movement under the same conditions, and less under the reverse. Ughetti* records, on the contrary, that in his observations the amplitude of the oscillations increased with the amount of pressure. Whilst the tremor of most morbid states is increased by intended movement, and that of the healthy state is probably induced by the same influence, it seems that in the trained hand the movement may, under these conditions, be reduced to a minimum, as a result of extreme delicacy of co-ordinative adjustment, either natural or acquired, and it may further be that some sense of security or guidance is derived from the performance of a well-defined and accustomed voluntary movement. The tremor was in general not appreciably influenced by the slight variations in pressure made. Tracings 1, 2, 3 and 4, Plates XXIV–XXVII, appear exceptional, in consequence of modifications dependent upon occupation and habitual movements.

The extent of movement was ordinarily smaller when the thumb and fingers were approximated in the attitude of prehension than when the fingers alone were applied to the tremograph (compare Tracings 2 and 4 with Tracings 1 and 3). This is probably due to the sense of support afforded by the former attitude and to the inhibitory influence of a well-defined voluntary act. In general, also, the number of movements in the same case, at the same observation, was smaller as registered with the aid of the tambours than when shown by the tremograph. This is probably owing to the greater delicacy of the latter, as the finer movements are lost in transmission through the tambours. The mental attitude of the subject seemed to have an appreciable influence upon the tremogram, the more intelligent and the more careful displaying greater movement under the same conditions than the unintelligent and the indifferent. Familiarity with the necessary manipulations on the part of the subject also brought with it greater steadiness.

The greatest frequency of movement computable was 10.7 per second, and was observed in a healthy individual and also in a hemi-

* Ughetti, loc. cit.

plegic; the smallest was 3, observed in a case of posterior spinal sclerosis. The general average of movement among all of the observations was 6.7. There was a good deal of uniformity of average under varying conditions when large numbers of cases were studied. On the other hand, the differences were more conspicuous among individual cases.

In a number of conditions, and especially in cases of paralysis agitans and of the spinal scleroses, the movements of symmetrical parts of the two sides of the body seemed to be practically synchronous (even when differences in the range of movement existed), in so far as comparative observations could be made (see Tracing 5, Plate XXVIII). When any difference existed between the movements of the two sides, it was slight and not constant.

Most of the movements displayed a want of regularity or rhythm. This was especially noticeable in the slighter and ill-defined movements, as those of health. Those of paralysis agitans particularly, as well as those in a case of diffuse sclerosis suggestive of paralysis agitans, displayed as a rule a tendency to regularity and rhythm. The occurrence of secondary or dicrotic waves, and even of tertiary waves, was often noted in tracings from cases of paralysis agitans (see Tracing 6, Plate XXIX). It was also observed in two cases of multiple sclerosis, one of which was suggestive in some respects of paralysis agitans. This peculiarity, which has also been noted by Wolfenden and Williams* and by Peterson,† will account for the wide variations noted in some cases. Of course the number of movements is greater when these secondary waves appear and less when they are suppressed. In this connection Wolfenden and Williams go so far as to contend that the special characteristics that distinguish clinically the various forms of tremor are to be traced to two causes: (1) an exaggeration of the amplitude of the normal vibration; and (2) the fusion of vibrations, which has the effect of producing a relatively slow tremor, generally of a rate corresponding to half that of the normal vibration.

It was hoped, among other things, that this study would aid in the differentiation between multiple sclerosis and paralysis agitans, but in this respect we were disappointed. Often easy, the diagnosis between these two conditions is at times exceedingly difficult. There

* Loc. cit.

† Loc. cit.

is reason for believing that the two affections are not unrelated both clinically and pathologically. At any rate it is probable that too much importance has been attached to the influence of rest and of voluntary effort respectively upon the tremor in the differentiation. In this connection it must not be forgotten that unequivocal cases of paralysis agitans may be unattended with appreciable tremor, either on account of its real absence or because of its concealment by the rigidity so often present.

We have been able to demonstrate graphically a clinical observation made by Dr. S. Weir Mitchell, that in cases of paralysis agitans, forcible extension of a finger of the shaking hand may temporarily restrain the movement of the hand (see Tracing 7, Plate XXX). That this interference is not merely mechanical is shown by the fact that the tremor soon recommences, even though the extension of the finger be maintained. Besides, similar restraint was sometimes observed when a finger of the opposite hand was thus extended. Some slight inhibition was at times induced by an effort of the will. Following the reduction in range of movement under these circumstances, there was usually an increase in the frequency. Closure of the eyes and of the opposite hand and the prick of a pin seemed to exercise only a transient disturbing influence, though occasionally an inhibiting effect was appreciable. In a case of choreal tremor, application of an Esmarch bandage to the arm was attended with a reduction in the range and rate of movement in the corresponding hand.

I present herewith a summary of the results of our study (Table A, p. 311) and append also a tabulation from various sources of those obtained by previous investigators in the study of tremor (Table B, p. 312). These tables show the wide variations of movement under all conditions, and strengthen the opinion already expressed, that special forms of tremor are not characterized by special frequency of movement. Indeed, it is probable that they present as well no other absolutely distinguishing feature.

CONCLUSIONS.

From our observations I think the following propositions are justified:

(1) All muscular movements are made up of a series of elementary

contractions and relaxations in alternation, which may be appreciable as tremor in conditions of both health and disease.

(2) The differences between different tremors are of degree rather than of kind, *i. e.* no one form of tremor is distinctive of any one disease or group of diseases.

(3) No definite relation exists between one form of tremor and any other.

(4) The frequency of movement is in inverse ratio to the amplitude and *vice versâ*.

(5) Habitual movements are performed with greater freedom from tremor than unusual movements.

(6) There is no material difference between the movements of the two sides of the body, except as related to Proposition (5).

DESCRIPTION OF PLATES XXIV–XXX.

See description in text, pp. 306-309.

(The tracings are to be read from left to right.)

Tracing 1 (tremograms).—From a watchmaker in health, 44 years old. *a*, the tremor attending delicate application with the right hand of a pair of forceps to the elastic diaphragm; *b*, the tremor from pressure of 1 oz. with the free fingers; *c*, that from a pressure of 2 oz.; *d*, that from a pressure of 4 oz. The broken straight lines represent time in seconds. The range of movement is greater as the pressure increases.

Tracing 2.—The curves are from the same case as Tracing 1 and were made under the same conditions, except that the fingers, above on the diaphragm, were approximated toward the thumb, below on the metallic plate, in the attitude of prehension.

The range of movement is distinctly less throughout than in Tracing 1.

Tracings 3 and 4 represent the same conditions as Tracings 1 and 2 respectively, except that the fingers of the left hand instead of the right were employed. The range of movement is in each instance greater with the left hand. The same relation as to range of movement holds between Tracings 3 and 4 as between Tracings 1 and 2.

Tracing 5 (two tambours).—From a case of paralysis agitans. Shows synchronism. The upper curve represents the tremor of the left hand, the lower that of the right. The broken straight line represents time in seconds.

Tracing 6 (two tambours).—From a case of paralysis agitans, in which the tremor preponderates upon one side. Shows dicrotism. The upper curve represents the tremor of the right hand; the lower, that of the left. The broken straight line represents time in seconds.

Tracing 7 (two tambours).—From a case of paralysis agitans. Shows the restraining influence of extension of the little finger of the tremulous member.

TABLE A.—Summary.

	Tremograph.						Tambours.					
	Right.			Left.			Right.			Left.		
	Max.	Min.	Aver.	Max.	Min.	Aver.	Max.	Min.	Aver.	Max.	Min.	Aver.
Health	10.0	4.5	7.0	10.7	4.0	6.7	..	..	..	..	..	..
Senility	8.5	5.2	6.8	8.0	5.2	6.6	..	..	..	..	..	..
Paralysis Agitans	8.9	5.2	6.3	8.5	5.0	6.3	7.3	4.5	5.5	7.8	4.5	5.5
Multiple Sclerosis	8.5	7.3	7.5	9.3	6.1	7.3	7.6	4.5	6.4	8.0	4.0	6.0
Diffuse Sclerosis	7.0	6.0	6.7	7.0	6.0	6.6	..	..	..	..	..	..
Posterior Sclerosis	5.0	3.6	4.4	5.3	3.0	4.4	..	..	..	..	..	..
Postero-Lateral Sclerosis	..	..	6.0	..	..	6.0	..	..	..	..	..	..
Hysteria	10.0	5.4	8.0	9.5	4.9	7.3	7.5	6.4	7.0	..	..	..
Neurasthenia	9.0	4.5	7.0	8.9	4.8	7.0	..	..	..	..	..	..
Exophthalmic Goitre	10.0	4.7	7.4	9.0	4.4	6.9	..	..	..	..	..	..
Writer's Neurosis	8.5	5.4	6.9	8.8	5.9	7.6	..	..	..	..	..	..
Melancholia	7.3	4.7	6.3	5.9	5.5	5.6	..	..	..	..	..	..
Right Hemiplegia	..	..	..	5.5	4.0	4.8	..	..	..	10.0	8.3	9.2
Left Hemiplegia	10.7	9.0	9.6	6.0	5.5	5.6	10.5	9.0	9.8	..	..	8.5
Chorea	5.1	5.0	5.0	..	..	5.0	..	..	3.9	4.0	3.6	3.8
Goitre	8.0	5.5	7.3	10.0	5.0	6.4	..	..	..	..	..	..
General Neuritis	7.5	5.2	6.5	7.5	5.2	6.6	..	..	..	..	..	..
Chronic Alcoholism	9.0	8.0	8.5	8.5	8.0	8.3	..	..	..	..	..	..
Pendulum Tremor	..	..	..	..	..	..	..	..	..	6.2	5.8	6.1
Arsenical Poisoning	7.5	7.4	7.5	..	..	6.8	..	..	..	..	..	4.9
Torticollis	..	..	..	..	..	..	..	..	..	..	..	7.6

Head.	Max.	Min.	Aver.
Lateral.	4.6	3.3	4.4
Ant.-Post.	3.9	3.3	3.6

Head.	Max.	Min.	Mean.
	7.9	7.6	7.8

TABLE B.

	Health.	Senility.	Paralysis Agitans.	Multiple Sclerosis.	Diffuse Sclerosis.	Posterior Sclerosis.	Postero-Lateral Sclerosis.	Hysteria.	Neurasthenia.	Exophthalmic Goitre.	Writer's Neurosis.	Melancholia.	Right Hemiplegia.	Left Hemiplegia.	Chorea.	Goitre.	General Neuritis.	Chronic Alcoholism.
Dana	10.0	5.0	3.0–6.1	..	..	8.0–8.6	..	5.0	10.0	8.0–9.5	..	..	..	..	..	..	..	6.2
Peterson	..	..	3.5–5.6	4.6–6.3	..	..	..	7.6–7.8	7.4	8.7–12.0	..	..	..	..	..	..	..	8.5–11.0
Wolfenden and Williams	..	5.5	5.1	5.8	..	..	..	..	..	10.8–11.5	..	..	..	..	..	..	..	..
Dutil	..	4.0–5.5	5.0–6.0	4.0–5.5	..	..	..	5.5–7.5	..	8.0–9.5	..	..	..	..	..	..	..	8.0–9.0
Fernet	..	..	..	3.0–5.0	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Gowers	..	..	4.8–7.0	6.0–7.0	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Charcot	..	..	4.0–5.0	7.0–10.0	..	..	..	5.0–7.0	..	..	..	..	..	..	..	..	..	..
Marie	..	4.5–5.5	5.0	..	..	..	..	..	..	8.0–9.0	..	..	..	..	..	..	..	..
Péré	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Horsley	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Ewald	..	..	5.0	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Grashey	..	..	4.1–5.3	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Huber	..	..	3.4–5.6	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Eshner	6.9	6.7	5.9	6.8	6.8	4.4	6.0	7.4	7.1	7.2	7.3	6.0	7.0	8.4	4.5	6.9	6.6	8.4

	Pendulum Tremor.	Arsenical Poisoning.	Torticollis.	Myelitis.	Progressive Muscular Atrophy.	Hemiplegia with Epilepsy.	Hemiplegia Embolism.	General Paresis.	Mercurial Poisoning.	Saturnine Poisoning	Delirium Tremens.	Lateral Sclerosis.	Hereditary Tremor.	Quinin.	Epilepsy.
Dana	..	..	..	5.0–6.0	5.0	4.8–5.0	10.0–12.0	..	..	..	..	6.0	8.0–9.0	10.0	8.5–8.8
Peterson	..	..	..	..	..	..	..	..	..	..	5.6 -6.5	6.0	..	..	10.0
Wolfenden and Williams	..	..	..	..	..	..	..	..	..	..	..	5.5	..	..	..
Dutil	..	..	..	..	..	..	..	8.0–9.5	..	..	..	..	..	..	..
Fernet	..	..	..	..	..	..	..	..	5.0	6.0	..	..	..	..	..
Gowers	..	..	..	..	..	..	..	10.0–12.0	..	..	..	..	..	..	..
Charcot	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Marie	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Péré	..	..	..	..	..	..	..	..	..	..	..	..	..	..	10.0
Horsley	..	..	..	..	..	..	..	..	..	..	..	8.0–10.0	..	..	..
Ewald	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Grashey	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Huber	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Eshner	6.1	6.4	7.6	..	..	..	..	..	..	..	..	..	..	..	..

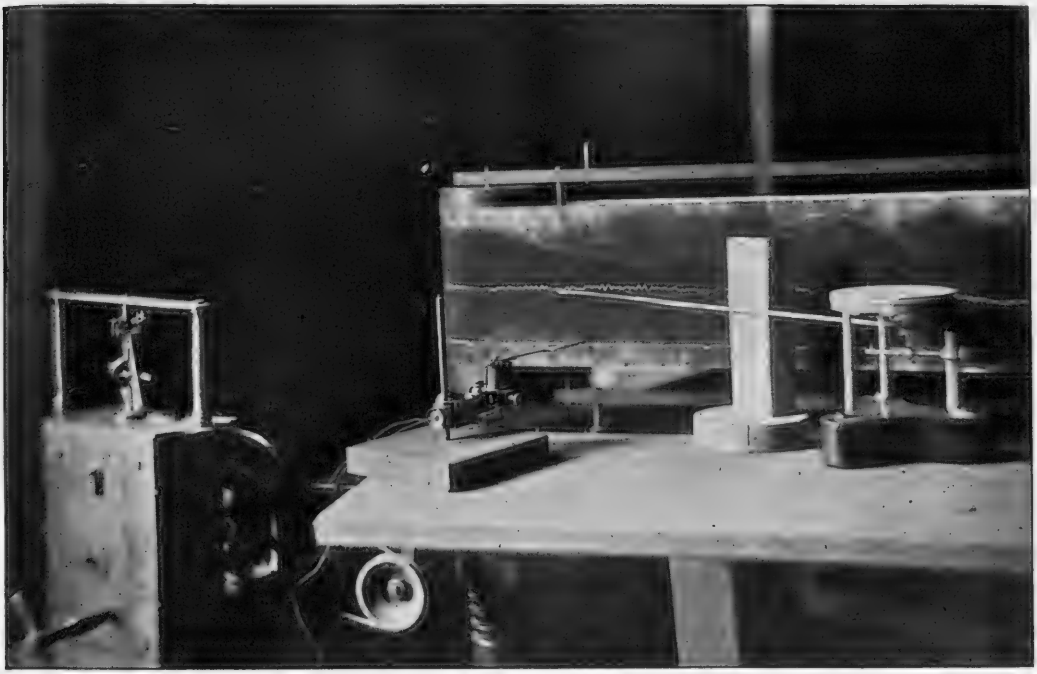


FIG. 1.

TREMOGRAPH WITH KYMOGRAPHION.

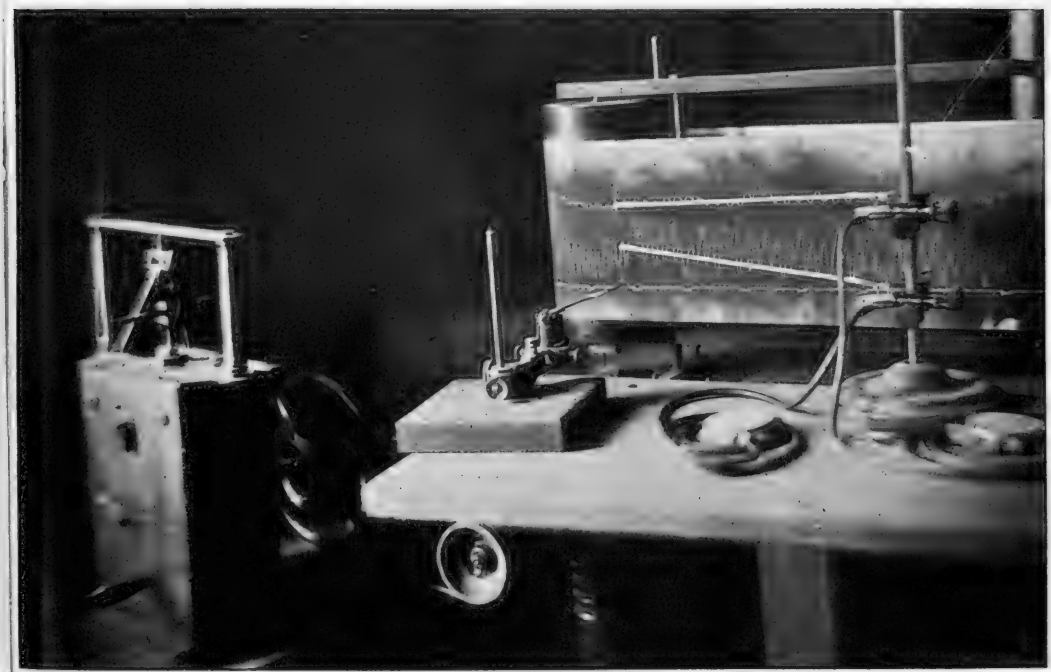
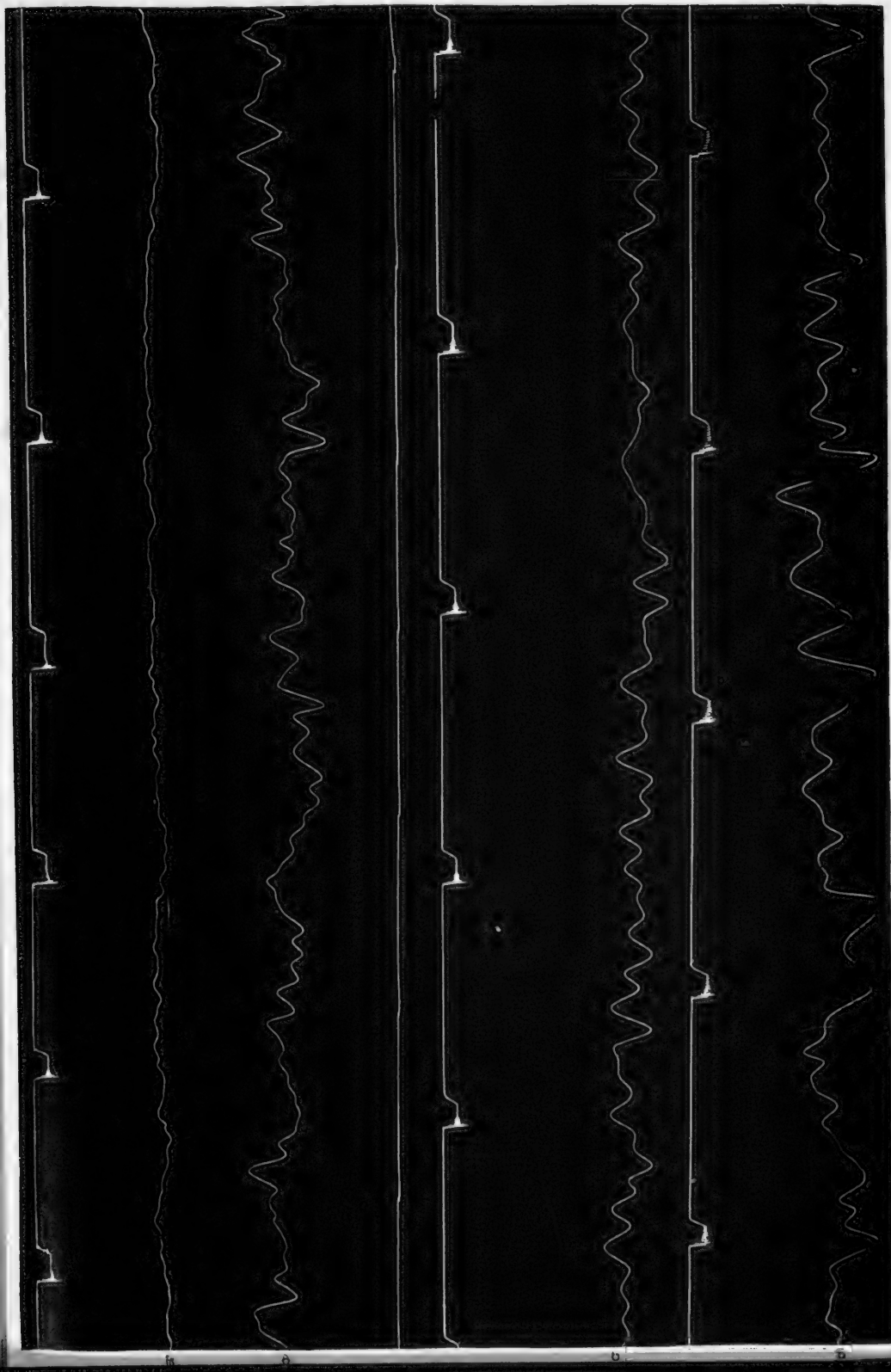
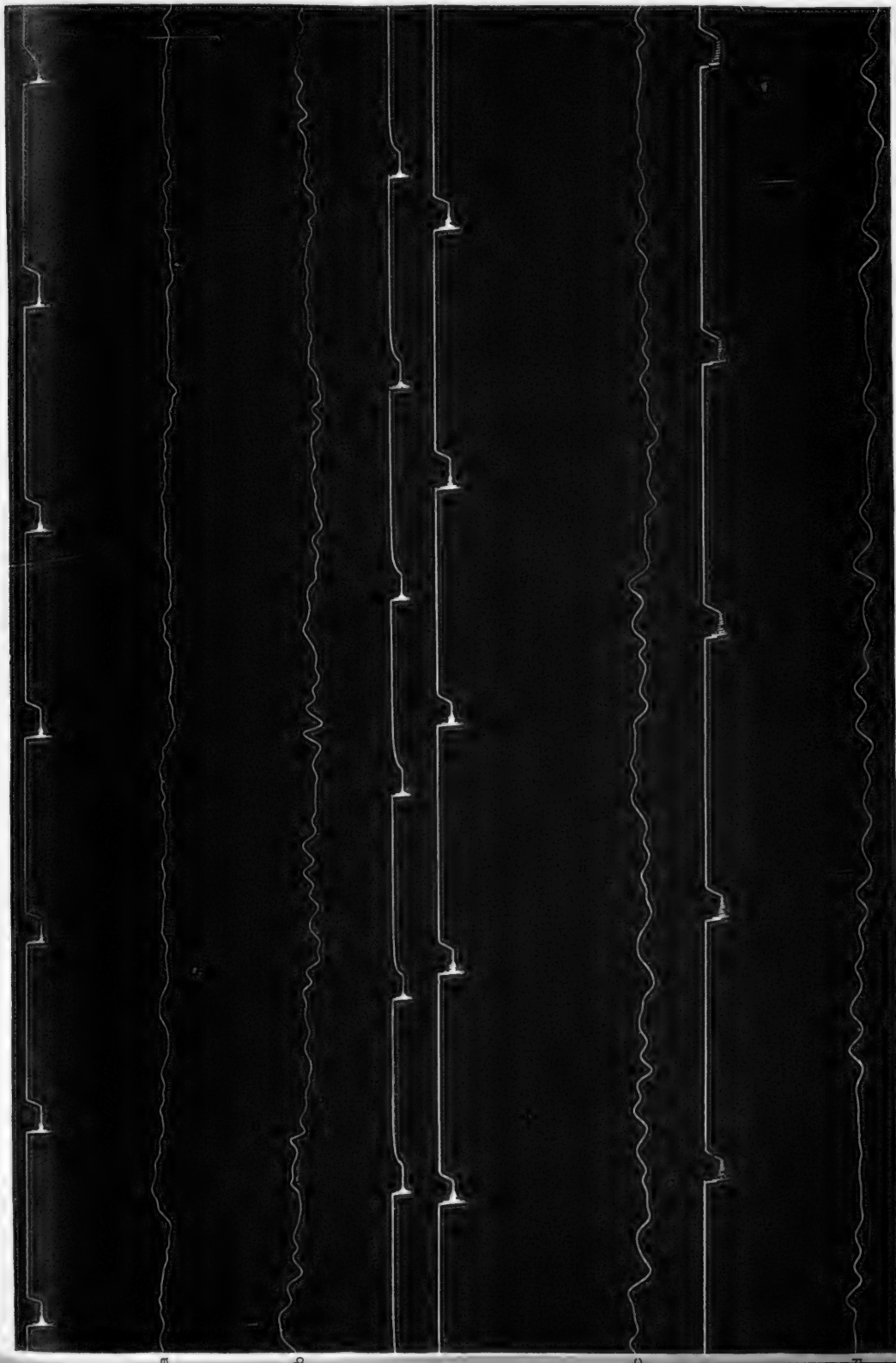


FIG. 2.

TAMBOURS WITH KYMOGRAPHION.

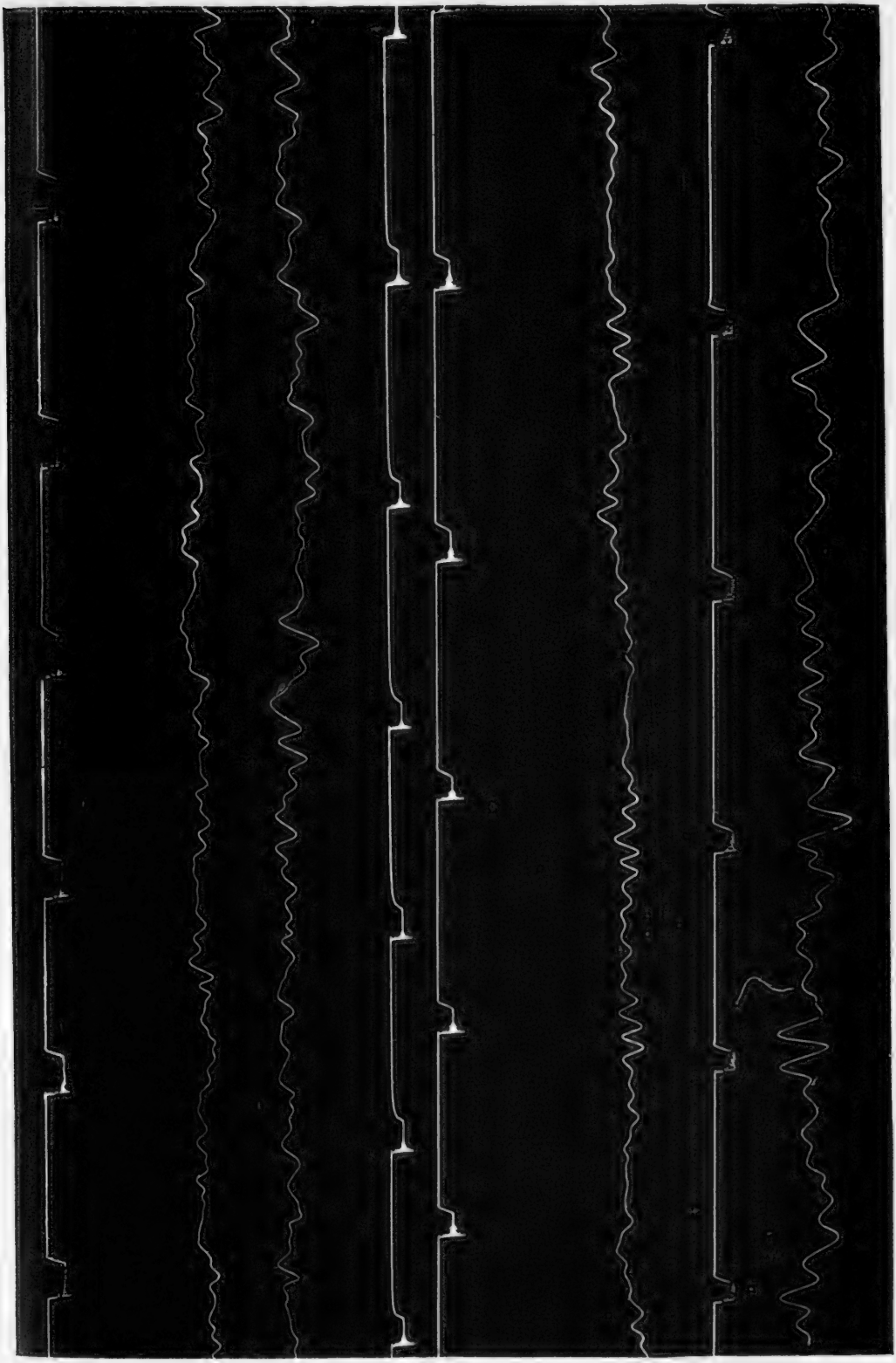


TRACING 1.



TRACING 2.

TRACING 3.



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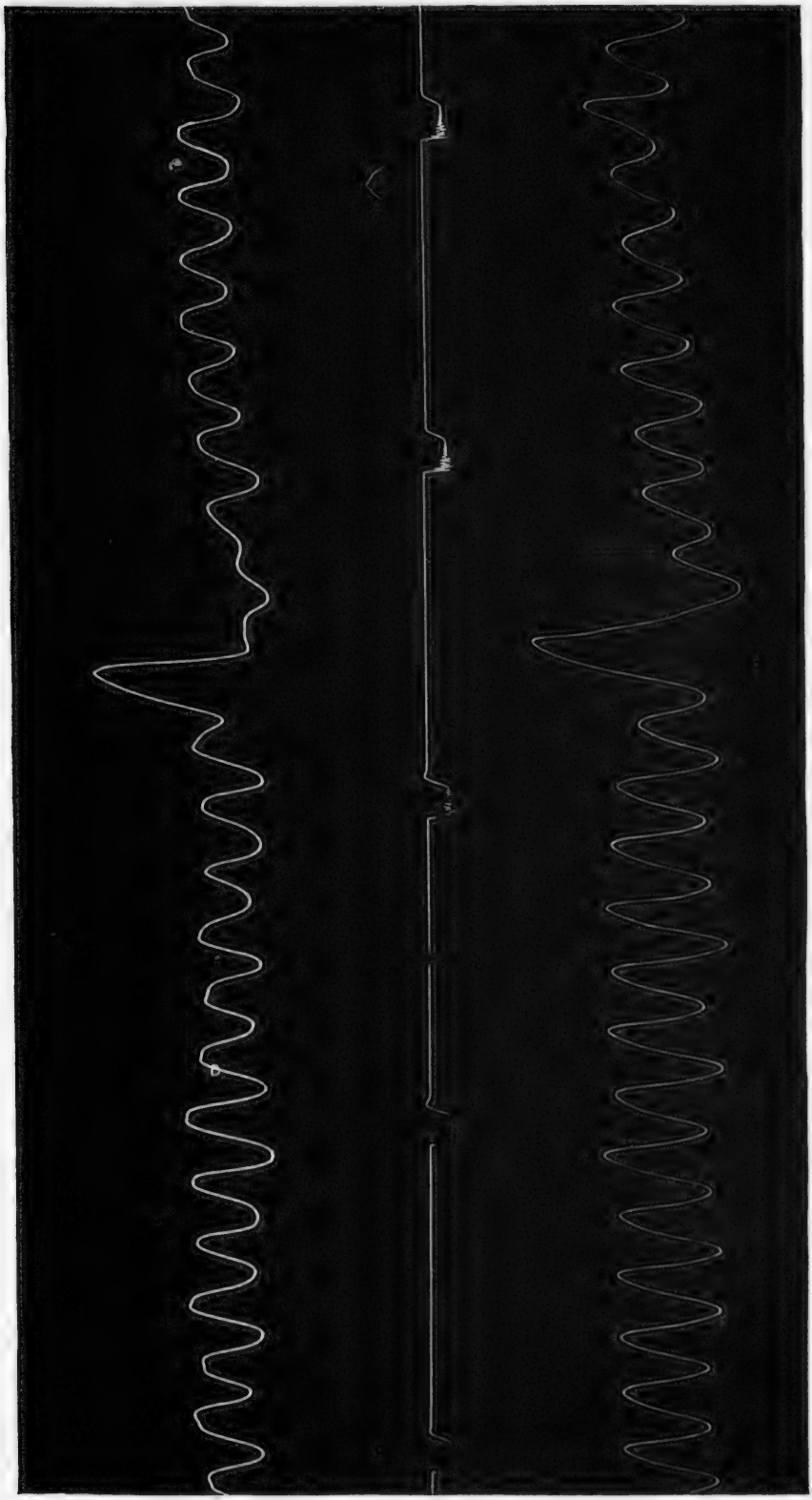

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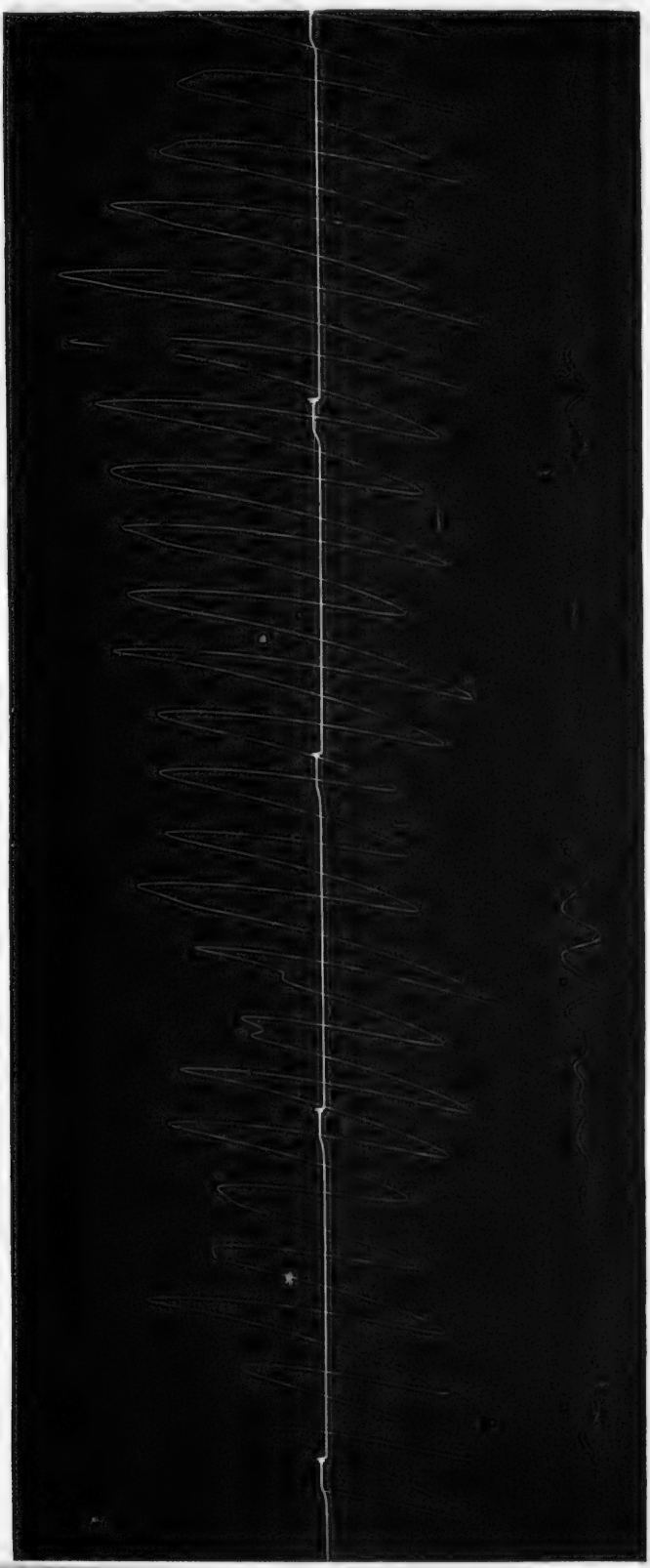

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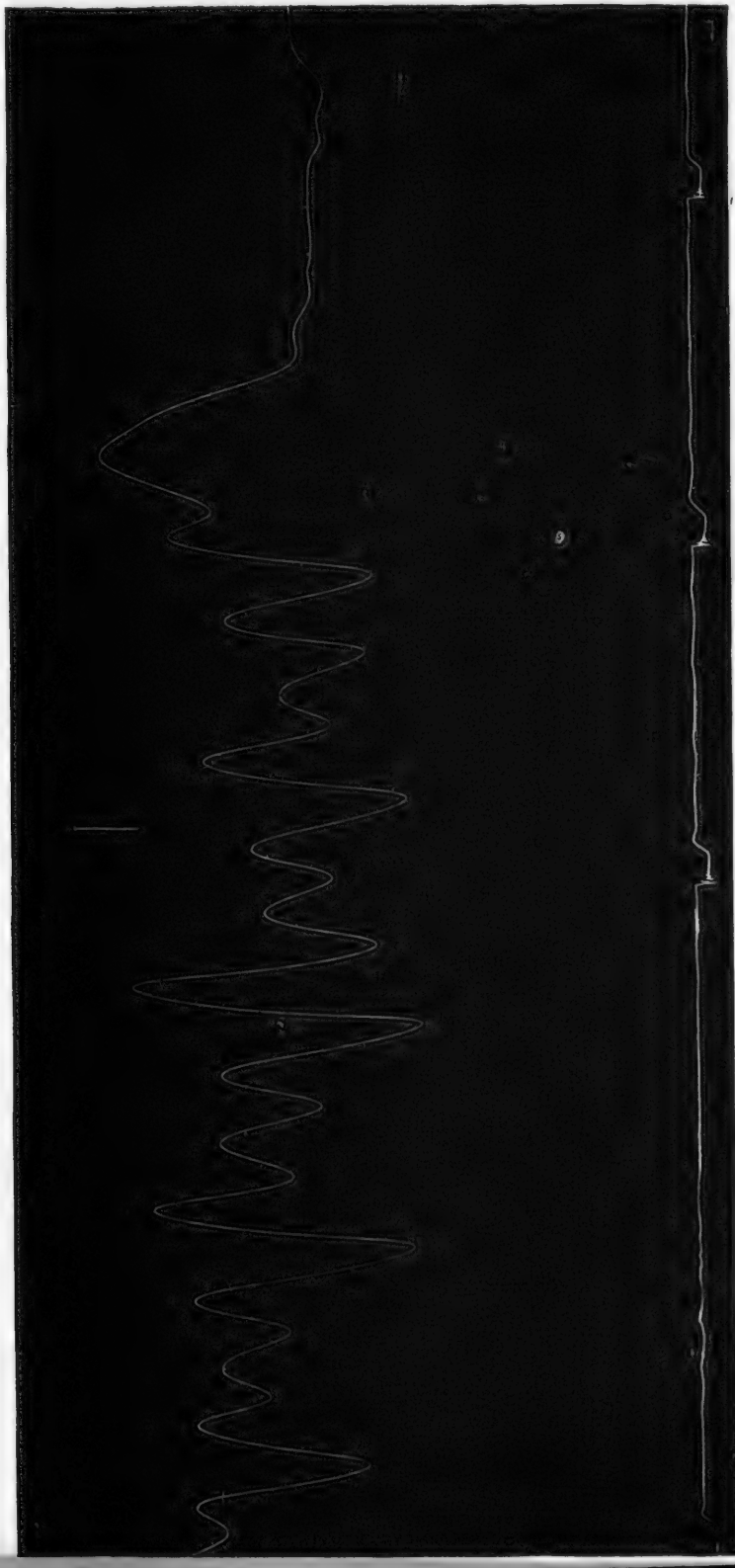


TRACING 7.

A CONTRIBUTION TO THE PHYSIOLOGY OF SLEEP, BASED UPON PLETHYSMOGRAPHIC EXPERIMENTS.

By W. H. HOWELL.

(*From the Physiological Laboratory of the Johns Hopkins University.*)

PLATE XXXI.

The primary object of these experiments was to determine the variations in volume of the arm as measured by a water plethysmograph during the entire period of normal sleep. The experiments were begun some years ago by Messrs. Bardeen and Nichols, who were at that time students in this laboratory. Their work gave them some very interesting curves, showing the sensitiveness of the vaso-motor centre to sensory stimuli not sufficiently strong to awake the subject experimented on, but they were unable to obtain a satisfactory plethysmographic record of an entire sleep period. This latter point I have endeavored to complete by experiments made upon myself at various times within the last few years. At first a large plethysmograph was used, measuring the changes in volume of nearly the entire arm; but this was afterwards abandoned, owing to the fact that the arrangements used to ensure immobility necessarily kept the arm in full extension, a position that quickly caused painful discomfort at the elbow joint and thus prevented normal sleep. The plethysmograph used in all the experiments here reported was much smaller, measuring the volume changes only in the hand and the lower part of the fore-arm, and allowing comfortable flexion and freedom of movement at the elbow. The apparatus employed was simple in character and can be sufficiently understood from a brief description.

DESCRIPTION OF APPARATUS.

The plethysmograph consisted of a glass cylinder of the usual form, 24 cm. in length and 10½ cm. in diameter, drawn out to a tube at the

far end and having two tubulatures. In one of these latter a stopper was inserted carrying a thermometer to measure the temperature of the contained water, and a glass tube which ended within the plethysmograph just below the stopper and gave exit to the air when the plethysmograph was filled with water. The other tubulature, which was at the lower surface of the plethysmograph when this apparatus was arranged for an experiment, was used to fill and empty the instrument. A piece of stiff rubber tubing was connected with the distal end of the plethysmograph. This tubing passed to the recorder and transmitted the water that flowed into or out of the plethysmograph as the arm contracted or expanded. The recorder used was the Bowditch* form. It consisted essentially of a test tube swung by a spiral spring, which was so adjusted as to keep the surface of the water in the test tube always at exactly the same level, the test tube pulling the spiral out as water flowed into it, and the spiral pulling the test tube up as water flowed out. To prevent the rotation of the test tube that arises from the twisting of the spiral, the movements of the spring were transmitted to the test tube by unspun silk fibres passing over a delicate pulley. The large end of the plethysmograph carried a sleeve of band-rubber tubing which fitted snugly the rounded portion of the fore-arm.

To keep the hand immovable within the plethysmograph, a modification of the device used by Shields† was employed. A hinged collar of hard rubber fitted round the thumb between the first and second phalangeal articulations. This was connected by a rigid rod with a similar though larger hinged collar, which fitted loosely the rounded portion of the middle of the fore-arm. This latter ring had a shoulder that pressed against the rim of the plethysmograph when the arm was in position, and thus prevented a thrust of the arm into the plethysmograph. The rubber sleeve covered this collar and was in turn pressed firmly against it by a larger double ring of hard rubber. One portion of this outside collar clasped the rim of the plethysmograph, while the second ring, rigidly connected with the first, fitted snugly on

* Bowditch, *Proceedings of the American Academy*, May 14, 1879.
† Shields, *The Journal of Experimental Medicine*, i, p. 74, 1896.

the band tubing and held it firmly against the inner collar. In this way the pulling of the arm out of the plethysmograph was prevented. A further use of the outside rings, as described by Shields, was to prevent any parting of the rubber sleeve where it extended from the edge of the plethysmograph to the arm. This purpose they accomplished by nipping the sleeve close down to the arm. The plethysmograph was suspended from the ceiling, according to the well-known device of Mosso, so as to allow free swing of the arm. The elbow was, in addition, supported by a sling of thick velvet, which was attached by cord to the chain swinging the plethysmograph. This cord was adjustable, so that when the subject lay upon the bed ready for an experiment, a position of the elbow could be found that was easy and comfortable. With the plethysmograph arranged in this way, the arm could swing freely from the shoulder and elbow without altering the position of the hand in the plethysmograph or changing the volume of water. Movements of the fingers gave, of course, pressure waves which affected the test-tube recorder, but such movements were only temporary and caused no permanent alteration in volume.

In preparing for an experiment, the hand and fore-arm were first thoroughly greased with vaseline to prevent the imbibition of water by the skin during the long immersion. The hand was then placed in the plethysmograph and the rubber sleeve and the holders were properly adjusted. Through the lower tubulature of the glass cylinder the apparatus and the tube passing to the recorder were filled with water warmed to 34° C., care being taken to force all air bubbles out of the tubing. It was found that the arm would keep the water in the plethysmograph very nearly constantly at 34° C. during a night's experiment. If the temperature varied slightly, that is, from 0.5 to 1° C., the latter being about the maximum variation observed, the alteration in volume of the water thereby produced was found to be so small as not to influence perceptibly the quantitative value of the plethysmographic curve. The pen that marked the movements of the test-tube recorder was made to write upon the blackened surface of the drum of a kymographion which was moved slowly by clock-work,

making one entire revolution in about twelve hours. In the same vertical line with the test-tube pen there was arranged an electric signal connected with a clock and marking intervals of fifteen seconds. After the apparatus had been filled with water, the pressure of water upon the arm was adjusted by moving the test-tube recorder so as to place the surface of the liquid in it at or near the level of the middle of the glass cylinder, the exact level varying slightly with the position of the arm in the plethysmograph. The result aimed at was to bring the middle of the arm as it lay in the plethysmograph to zero pressure. Since it is obviously impossible, in a water plethysmograph, to have the entire arm free from positive or negative pressure, it would seem to be most desirable, theoretically, to have the zero pressure as nearly as possible at the middle of the portion of the arm used. Under these circumstances the positive pressure of an inch or two of water upon the under portion of the arm is counteracted by a similar negative pressure upon the upper portion. As Shields has shown in his paper, this point is one of considerable practical importance. If the entire arm is under slight positive pressure, a distinct diminution in volume results, apparently from the effect of this pressure on the superficial veins, while a negative pressure has the opposite effect. Practically, it was found that the best results were obtained when the point of no pressure was at the middle of the portion of the arm immersed in the water.

This whole difficulty can be obviated by using an air instead of a water plethysmograph. In an air plethysmograph the changes in volume of the arm cause a flow of air out of or into the cylinder, and the quantity of air displaced can be measured conveniently by a delicate counterbalanced spirometer. An apparatus of this kind was used in several experiments, but was afterwards abandoned, since, naturally, its accuracy depends very largely upon keeping the temperature of the air constant, and in all-night experiments this was not practicable. Even in shorter experiments the records are vitiated from a quantitative standpoint by the fact that a congestion of the arm causes a greater radiation of heat from the skin and *vice versâ*.

When the various details described above had been properly

arranged, the lights were lowered and the subject of the experiment, who lay upon a comfortable bed, attempted to go to sleep. During the entire experiment a watcher, who sat at a little distance, made copious notes of the movements of the sleeper and their effect upon the curve, and of any disturbing noises, from cabs in the street and the like, that seemed to affect in any way the record that was being taken.

I desire in this connection to express my great thanks to Dr. G. T. Kemp and Dr. Reid Hunt, who most kindly assumed this disagreeable task, and by their friendly interest in the work made possible what measure of success was eventually attained.

It was arranged between the sleeper and the watcher that if the former awoke at any time during the night he was to utter the word "awake," so that the fact might be indicated on the record. In some cases this indication was given satisfactorily, the sleeper remaining awake for a longer or shorter time in a drowsy condition, but finally falling asleep again, usually within a few minutes. In other cases, however, the return of consciousness on the part of the sleeper was not sufficiently complete to enable him to articulate the word "awake" satisfactorily. In some instances of this kind the sleeper subsequently remembered distinctly being awake and thought that he had given the signal agreed upon; but the notes of the watcher recorded only that the sleeper muttered unintelligibly. At other times the sleeper was conscious of being awake, but his mental condition was such that he considered it unnecessary to state the fact, or indeed felt an irritable objection to making an exertion to speak. This perverse condition was remembered afterward with regret upon full awaking, but at the time there seemed to be lacking on the part of the sleeper a full comprehension of his interest in the experiment. An interesting and rather unexpected fact with regard to these experiments was that in none of them did the sleeper have any conscious recollection of dreaming. The unusual and somewhat uncomfortable conditions of the experiments had led him to suppose that disagreeable dreams would trouble his slumbers.

By the method thus briefly described some twenty sleeping experi-

ments were made. Of these not more than four or five gave entirely satisfactory results, although many of the partially successful experiments gave interesting curves that confirmed some of the general conclusions drawn from the better experiments. The causes of failure were numerous, and some of them may be referred to here in a few words. One great difficulty at first was my inability to go to sleep under the unusual conditions of the experiment. If it had been possible to make a continuous series of experiments, it is probable that I would have become accustomed to the surroundings and this difficulty would have vanished. Owing to other duties, which need not be specified, a continuous series was impossible, and the experiments were made at intervals over a period of two years. In order to sleep easily under the unusual conditions I found it necessary to make myself very sleepy. This end was attained most satisfactorily by sitting up the greater part of the night previous to an experiment and taking a considerable, but not an excessive amount of out-door exercise on the day of the experiment. This procedure was usually effective in enabling me to fall asleep within ten or fifteen minutes after the beginning of an experiment. A second serious cause of trouble was the adjustment of the pressure of the rubber sleeve upon the arm. The sleeve must be sufficiently tight to prevent leakage of water, and yet must not compress the skin so as to lead to a passive congestion of the parts within the plethysmograph. Numerous experiments were spoiled for quantitative purposes by an excessive pressure of the rubber sleeve, although they gave some results that were of value. To obviate this difficulty, the arm, where the sleeve pressed upon it, was coated thickly with vaseline, and the sleeve itself was selected of such a size as just to prevent a leakage. This size was determined by actual trial. The test of success in this matter, which was regarded as the best under the circumstances, was the fact that at the end of the experiment, upon awaking from sleep, the arm returned quite, or approximately, to the size it had shown at the beginning of sleep. A third difficulty, of much less importance, lay in the fact that the experiments were conducted in a laboratory adjacent to a public street, the noise of cable cars and passing cabs probably being responsible for some of the smaller changes in the curves.

DESCRIPTION OF THE CURVES OBTAINED, SHOWING THE CHANGES IN VOLUME OF THE ARM DURING SLEEP.

Examples of these curves are given in Figures 1 and 2, Plate XXXI, which represent two of the successful experiments. The details concerning these experiments are given in the descriptive legends accompanying the figures, and only the general features common to these and other curves need be dwelt upon here. It will be seen that from the beginning of the experiment, which coincides with the moment the sleeper closed his eyes and attempted to go to sleep, the curve begins to fall, that is, the portions of the arm in the plethysmograph undergo dilatation. Somewhere upon the descent of the curve the condition of sleep comes on. The exact time it was of course impossible to mark, but in these two experiments, and in most of the others, it may be asserted safely that the subject was asleep within fifteen minutes at the most. After sleep appears, the curve continues to sink with fair regularity, reaching its lowest point at one to one and a half hours after the beginning of the experiment, at which time the dilatation of the arm attains practically its maximum extent. For the next hour or two the curve remains at this low level, with the exception of certain periodic and incidental alterations that will be referred to later. After this period the curve usually begins to show a steady rise, which, for the first hour or longer, is quite gradual, but during the last half-hour or so preceding the final conscious awaking becomes much more rapid, so that at the time of awaking the volume of the arm is nearly or in some cases quite the same as at the moment of going to sleep. The time intervals specified here apply to a sleep lasting only from four to four and a half hours. If the period of sleep had been longer there would doubtless have been a longer interval after the maximum fall of the curve had been reached, before the rise began, and probably a longer continuance of the slow constriction. In the two curves given, the moment of final awaking is indicated by the mark ×.

In addition to this general course of the curve, it will be noticed that numerous secondary variations are exhibited. These minor variations fall into two classes: sharp oscillations, lasting a comparatively brief time and very variable in extent, and longer, nearly

periodic waves. The latter were present quite constantly in all the curves recorded. The waves had, roughly speaking, an hourly period, the extreme limits of duration varying perhaps between half an hour and an hour and a half. They constitute one of the most characteristic features of the plethysmographic curve. The sharper and briefer oscillations were found in the great majority of cases to be connected either with external stimuli, such as noises, or in some experiments, electrical stimulation; or with movements of the sleeping subject, such as sighs or movements of the arms, legs or head. An explanation of these two classes of variations in the curve will be suggested when the cause of the changes in volume of the arm is discussed. It should be added that the act of final, spontaneous awaking was always accompanied by a steep rise in the curve. The exact alteration in the volume of the arm varied greatly in the different experiments, although the portion of the arm measured was, in all cases, substantially the same. The precise amount of the volume changes was easily determined by calibrating the test-tube recorder. In the two curves reproduced in Figs. 1 and 2, the maximum dilatation was 18.5 cc. and 15.91 cc. respectively. In other experiments in which the conditions were equally favorable the dilatation was much less pronounced, being as small as 8 or 9 cc., while in two of the earlier experiments in which the conditions were not so good the maximum dilatation was $4\frac{1}{2}$ and $5\frac{1}{2}$ cc. respectively. Among the numerous experiments which were regarded as unsuccessful great variations were noticed. When the rubber sleeve pressed too tightly upon the arm or when the arm was under a negative pressure a steady dilatation ensued, owing apparently to a passive congestion of the arm. The dilatation in such cases was excessive and was not prevented by awaking, although before awaking there was a noticeable retardation of the dilatation, while at the moment of awaking the usual sudden constriction occurred, quickly followed, however, by a continuation of the slow dilatation.

EXPLANATION OF THE CHANGES IN VOLUME.

Mosso's* well-known plethysmographic experiments have shown conclusively that there is an enlargement of the limbs during sleep,

* Mosso, Ueber den Kreislauf des Blutes im menschlichen Gehirn, 1881; Die Temperatur des Gehirns, 1894.

an enlargement which he attributes to a vascular dilatation. He has also been able to show, from numerous very interesting observations upon individuals with defects in the skull wall, that there is, in general, a coincident diminution in the volume of the brain during sleep, and that upon awaking the volume of the brain increases, while the volume of the limb in the plethysmograph diminishes. So also in mental activity, such as takes place in solving problems in arithmetic, Mosso has shown that the variations in volume of the arm and the brain stand in reciprocal relationship to each other, the volume of the arm decreasing while that of the brain increases. So far as the effect of mental activity upon the volume of the limbs is concerned, this observation of Mosso's has been abundantly confirmed by others. In this laboratory we have obtained numerous beautiful examples of this effect in experiments made by Messrs. Bardeen and Nichols, and by Dr. Shields, the mental activity being aroused by sums in mental arithmetic, unexpected examinations in the case of students, or by discussions or arguments upon questions that interested the subject of experimentation. In his later works, Mosso is inclined to deny that there is an exact reciprocal relationship between the volume of the limbs and the volume of the brain, since he has made observations which convince him that the blood-vessels of the brain possess vasomotor nerves that are capable of altering independently the amount of blood flowing through this organ.

Experimental work on the lower animals, however, tends strongly to show that a definite relationship does exist between the circulation in the brain and general arterial pressure. The experiments of Gaertner and Wagner,* Roy and Sherrington,† Bayliss and Hill,‡ Reiner and Schnitzler,§ and others agree in showing by different methods that an increased flow of blood through the brain follows upon every rise of general arterial pressure and *vice versâ*. More than this, the results of recent careful work upon the brain circulation (see,

* Gaertner and Wagner, *Wiener med. Wochenschrift*, 1887.

† Roy and Sherrington, *Journal of Physiology*, xi, p. 85, 1890.

‡ Bayliss and Hill, *Journal of Physiology*, xviii, p. 334, 1895.

§ Reiner and Schnitzler, *Archiv fur exp. Pathol. u. Pharmakol.*, xxxviii, p. 249, 1897.

especially, Bayliss and Hill) go to show that the brain vessels possess no vaso-motor fibres, and that the volume of circulation through them is regulated passively by variations in arterial pressure in the remainder of the body. A vaso-constriction of parts of the body outside the brain sufficient to cause a rise of general arterial pressure tends to drive a greater quantity of blood under higher pressure through the brain, while a local or general vaso-dilatation of the blood-vessels sufficient to cause a fall in general arterial pressure causes a lessened flow through the brain. To this means of regulating the flow of blood through the brain we must add the effect of the accelerator and inhibitory nerves upon the heart beat. Other conditions remaining the same, an augmented heart beat must increase the blood flow through the brain as well as through other parts of the circulation.

The volume changes described in the present experiments must be interpreted as meaning a vaso-dilatation in the arm vessels, and indeed from what we know of the vaso-motor supply of the muscles and skin respectively, it is altogether probable that the dilatation is due mainly to a relaxation of tone in the skin vessels.* There is every reason to believe that a similar dilatation occurs over the cutaneous surface generally. This belief is borne out by the well-known fact that the skin is flushed and of considerably higher temperature during sleep, and is indicated also by the fact that in Mosso's† plethysmographic experiments upon the foot this limb was found to vary under the influence of mental activity in a way similar to that described for the arm. The amount of dilatation of the hand and the part of the fore-arm used in my experiments varied, in round numbers, between 8 and 18 cc. If

*The substance of this paper was communicated at a meeting of the American Physiological Society, December, 1896. At that time Dr. Meltzer suggested that the dilatation might be due in part to a relaxation in the tonicity of the skeletal muscles during sleep. This possibility must be admitted, but it is not definitely known how variations in tonicity in the striated muscles affect the blood capacity, and in any case it is not probable that this factor could explain the increase in volume obtained, owing to the small muscular mass in the parts used, namely, the hand and the lower portion of the forearm.

† Mosso, Die Temperatur des Gehirns. Leipzig, 1894.

the dilatation in other parts of the skin is proportional in amount, it is probable that during sleep a very considerable fall of general arterial pressure takes place, and this conclusion is verified by the direct experiments made by Tarchanoff* on sleeping dogs. Tarchanoff observed that in young dogs in which sleep occurred while the animal's blood pressure was being recorded, there was a fall of general arterial pressure during sleep amounting to from 20 to 50 mm. of mercury, the pressure returning to normal when the animal awoke.

Taking these facts together, it seems highly probable that the plethysmographic curves described in this paper may be interpreted to mean, in general, that during sleep there is a diminished peripheral resistance in the skin area, and therefore a lower arterial pressure and a smaller blood flow through the brain. Or, assuming that the volume of the brain circulation stands in reciprocal relationship to the volume of the arm, the changes in the amount of blood circulating through the brain during sleep may be stated as follows: At the commencement of the period preparatory to sleep the blood flow through the brain begins to diminish in quantity, owing to the fall in arterial pressure, and for a period of an hour or more after sleep has appeared the blood flow grows less and less, following the continued diminution in arterial pressure. After reaching its minimum, the volume of the brain circulation remains practically constant, with the exception of the temporary variations which have been referred to previously, for one or two hours, or possibly longer, if the period of sleep lasts for a greater time than was obtained in these experiments. The blood flow through the brain begins then to increase gradually, following the rise in blood pressure produced by the slow constriction of the skin vessels, and this increase becomes much more rapid for the short period of one-half to three-quarters of an hour preceding spontaneous awaking. At the time of awaking, therefore, the volume of the blood flowing through the brain is approximately the same as at the time sleep appeared.

One may ask whether the dilatation of the blood-vessels during sleep affects the visceral organs as well as the superficies of the body.

* Tarchanoff, *Archives ital. de Biologie*, xxi, p. 318, 1894.

The question is a difficult one to answer satisfactorily, but it seems probable from the incomplete facts in our possession that the internal organs do not share in this dilatation; it is possible, on the contrary, that the volume of blood circulating through the internal organs is diminished rather than increased in quantity. Mosso, in his interesting experiments on the temperature of the brain, has shown that the temperature of the rectum falls slowly during sleep, following a curve nearly parallel to that of the brain. The temperature curves of the brain and the rectum, in fact, show a striking similarity to each other in their general features, and also to the curve of vascular dilatation of the arm during sleep obtained in my experiments, the minimum temperature agreeing closely in time with the maximum dilatation of the superficial vessels. It is, perhaps, permissible to suggest that the general relaxation of the skin vessels, with the consequent lowering of blood pressure, diverts blood not only from the brain, but also from the rectum, and thus causes the gradual fall of temperature. It is stated also by Roemer* that the temperature of the skin of the hand remains always during the day below the average and during the night above the average, while in the rectum the case is just the reverse. If the other parts of the alimentary canal behave similarly to the rectum in losing temperature during sleep, it would seem probable that less blood rather than more blood circulates through them during sleep. Upon awaking his subjects Mosso obtained a gradual and parallel rise of temperature in the rectum and in the brain, just as in awaking a subject with his arm in a plethysmograph there is a constriction of the vessels in the arm. As further evidence in the same direction, it may be recalled that the secretions and movements of the alimentary canal and the secretions of the kidney and the liver are said to be diminished during sleep, and these facts point to a lessened blood supply rather than to an increased blood supply during this period. Moreover, from the data that I have obtained of the actual increase in volume of the arm during sleep, and from the figures given by Mosso and others of the amount of constriction

* Roemer, quoted from Hermann's Handbuch der Physiologie, Bd. iv, ii, p. 385.

of the arm during mental activity, it is evident that if similar figures hold for the entire cutaneous surface, the variations in skin circulation under these conditions are far too great to justify the supposition that the large increase or decrease in blood capacity of the skin is compensated by changes in the volume of blood in the brain alone. Our best evidence, in fact, goes to show that the actual volume of blood in the brain can undergo only small variations at most, and the large changes in the amount of blood in the limbs during sleep or mental activity must be compensated by opposite variations in the volume of the circulation elsewhere. It seems possible, therefore, that simultaneously with the dilatation of the limbs during sleep there is a lessened volume of blood in the viscera, but experimental evidence is requisite before positive statements can be made on this point.

THE MINOR VARIATIONS IN THE PLETHYSMOGRAPHIC CURVE.

The slow, wave-like variations in the curve that have been spoken of on page 320 are well illustrated in the two curves printed as Figs. 1 and 2, Plate XXXI. These long oscillations, as has been said, were found in all my records and form a characteristic feature of the sleep curve. I do not know that this phenomenon has been noticed before. Mosso* speaks of spontaneous changes in the volume of the arm that do not depend upon external stimuli or respiratory movements, but these changes, if I understand his descriptions correctly, are of much briefer duration than those now under consideration. It can scarcely be doubted that these slow, nearly periodic constrictions and relaxations of the volume of the arm are due to a slowly developing vaso-constriction of the vessels in the arm followed by a gradual dilatation. The very gradual development of the waves, lasting in most cases for about one hour, makes it improbable that they are owing to the action of external stimuli or to internal stimuli, such as psychical processes in the cerebrum. While it is not possible to give any experimental proof of their causation, the general character of the curves suggests at once that they are caused by rhythmic changes in the

* Mosso, Ueber den Kreislauf des Blutes im menschlichen Gehirn, p. 95.

vaso-motor centre, and indeed, if the assumptions made as to the sleep curve in general are correct, to a rhythmic increase and relaxation of tone in that part of the vaso-constrictor centre controlling the vessels of the skin. The ultimate cause of this variation does not appear upon the surface, but rhythmic changes of this sort seem to be characteristic of the vaso-motor centre, as is seen, for instance, in the well-known Traube-Hering waves. In fact, the variations which we are discussing here resemble closely the Traube-Hering waves in their general character, with the exception that they are of much longer duration.

The shorter, more numerous and more irregular oscillations of the sleep curve are perhaps more easily explained. These changes, as may be seen from the records published, are very variable in extent. Many of them were clearly traceable to external stimuli, such as noises or, in one series, to electrical stimulation of the skin. Some of them were not, so far as could be determined, connected with any obvious cause; they were apparently spontaneous and possibly, as Mosso suggests, in what I consider similar cases, were owing to psychical processes of an unconscious or, at least, of an unremembered character. But most of the changes in question were undoubtedly connected with deep respirations, as in sighing, or with movements of other parts of the body, such as the head, feet or other arm. It may be asserted safely, I believe, that these movements did not affect the plethysmographic record by causing actual movements of the arm into and out of the glass cylinder, nor were the changes in question produced by simultaneous movements of the parts of the arm within the apparatus. In the first place, the arm was so fastened in the swinging and freely movable plethysmograph that movements into and out of the cylinder were practically prevented; and, secondly, if a retraction or thrust of the fore-arm had been possible to a slight extent, the character of the change in the plethysmographic record would have been entirely different. The same remark holds true for movements of the fingers within the plethysmograph. In either case the effect upon the plethysmograph curves would be sharp and sudden. Movements of the fingers, for instance, would cause the pen of the record-

ing test tube to move rapidly up and down, producing upon the slowly moving drum, which required twelve hours for a complete revolution, only a sharp up-and-down stroke. This effect was not infrequently observed during the course of an experiment, and an example may be seen in the curve shown in Fig. 1, Plate XXXI.

The changes which we are describing were, on the contrary, characterized by a fairly rapid rise of the curve, that is, a constriction of the arm, which was followed by a relatively gradual return to the original level. Indeed, even the comparatively rapid rise when observed with the eye was nothing like so sharp as that caused by movements of parts within the plethysmograph. The pen mounted slowly to its maximum and dropped back much more slowly. In fact, the waves in the record made by movements of muscles in other parts of the body resembled in every respect those caused by electrical or sound stimuli. These latter are unquestionably vaso-motor changes, and we must suppose that the waves produced by muscular movements are also due to reactions upon the vaso-motor centre. The physiological mechanism by means of which the movements of the foot, for example, may cause a vascular constriction in the skin of the fore-arm and hand is not easily understood. It is possible, of course, that the effect may be owing to a sensory reflex of a pressor character, originating from an irritation of sensory fibres in the part moved, but this explanation does not seem probable, particularly as it has been shown that stimulation of muscular nerves produces usually a depressor effect, that is, a vascular dilatation.* It seems possible to the author that discharges from the motor cortex, like other forms of cerebral activity, affect directly the vaso-motor centre and bring about a constriction that is more or less marked, according to the condition of the vaso-motor centre, being especially pronounced, perhaps, during sleep, when a part of the vaso-motor centre is in a condition of relaxed tone. This suggestion is supported, to some extent, by the experiments of Stricker† and of Danilewsky‡ upon the effect of stimulating

* See Hunt, *Journal of Physiology*, xviii, p. 381, 1895.

† Stricker, quoted from Hermann and Schwalbe's *Jahresberichte*, xv, p. 44, 1886.

‡ Danilewsky, Pflüger's *Archiv fur die gesammte Physiologie*, xi, p. 136.

the motor area in dogs. According to these observers, stimulation of the cortex, in certain parts at least of the motor areas, is accompanied by a rise of blood pressure. It may be interesting to add that in many of the sleep experiments the oscillations of the curve became more pronounced toward the end of the sleep, particularly during the half-hour or so preceding awaking, when the constrictor centre was rapidly regaining its normal tone.

RELATION OF THE PLETHYSMOGRAPHIC CURVE OF SLEEP TO THE CURVES OF INTENSITY OF SLEEP.

The intensity of sleep in the adult during normal slumber has been measured by Kohlschütter,* by Mönninghoff and Piesbergen,† and by Michelson.‡ The method used was substantially the same in all of these investigations; that is, the depth of unconsciousness was measured in terms of the intensity or energy of the sound necessary to awake the sleeper. In Kohlschütter's curve it appears that immediately upon going to sleep the intensity of unconsciousness increased rapidly to a maximum, which was reached at the end of the first hour. The curve then fell very rapidly during the next half-hour, and more gradually in the succeeding hour, so that two and a half hours after the beginning of sleep the curve was nearly at the base line, or, in other words, only slight stimuli were necessary to awake the sleeper. From this point to about the eighth hour the arm gradually approached the base line, and during this entire period the depth of unconsciousness was but slightly below the threshold. The curve obtained by Mönninghoff and Piesbergen is, in its general features, similar to that obtained by Kohlschütter, with the exception that the maximum intensity was reached one and three-quarters of an hour after the beginning of sleep, and a second much lower rise of intensity was noticed between the fifth and sixth hours. In detail their curve shows that during the first hour the intensity was so slight as to be scarcely measurable by

* Kohlschütter, *Zeit. f. rat. Med. 3te Reihe*, xvii, p. 209, 1863. Also xxxiv, p. 42, 1869.

† Mönninghoff and Piesbergen, *Zeitschrift für Biologie*, xix, p. 114, 1883.

‡ Michelson, quoted from Wundt's Physiologische Psychologie, 4th ed. 1893.

their method, but that beginning at an hour and a quarter after sleep the intensity rose very rapidly, reached its maximum at an hour and three-quarters, and then sank as rapidly during the next half-hour. From two and a quarter to four and a quarter hours the curve fell more gradually, then showed a slight rise, reaching its maximum at five and a half hours, and subsequently dropped slowly to the base line.

The plethysmographic curve described in this paper shows no resemblance to either of these curves except during the first period. Upon the interpretation of the plethysmographic curve given by me, it may be said that during the period of rapidly increasing intensity of sleep, especially as illustrated in the curve by Kohlschütter, there is a corresponding diminution in the volume of blood flow through the brain, and the maximum of intensity of sleep corresponds apparently with the minimum flow of blood through the brain. But from this point onward the intensity curve and the plethysmographic curve show no resemblance to each other. While the irritability of the brain cortex rapidly approaches the normal, and after the second to the third hour lies almost at the threshold, the anæmic condition of the brain remains practically as it was during the period of deepest sleep. During this period the circulatory conditions in the brain are apparently not connected with the depth of unconsciousness of the sleeper. Some interesting conclusions that may be drawn from this comparison of the two curves will be referred to in the subsequent section discussing the causation of sleep.

It seemed to the writer that in view of the discrepancy between the two curves and the fact that the curves published by Kohlschütter and by Mönninghoff and Piesbergen represent results obtained from a very limited number of individuals, it was advisable to test his own curve of intensity to ascertain whether it conformed to the types described by the authors named. Experiments were accordingly made in this direction, the results of which, although not sufficiently complete for the publication of details, showed clearly that in the writer the normal intensity of sleep follows in general the curve described by Kohlschütter, in that the maximum is reached within the first hour or so after the beginning of sleep, and that from this point the

curve drops at first rapidly and then more slowly to the base line, although it does not approach so nearly to the base line in the second to the third hour and subsequently as in Kohlschütter's curves. It would seem, therefore, that the want of parallelism between the intensity and the plethysmographic curves mentioned above is probably a normal occurrence. It may be well to add that in my experiments upon the intensity of sleep I adopted a new method. The intensity of sleep was measured by the strength of the current from an induction coil necessary to awake the sleeper. The amount of the induced current was measured directly in scale deflections of a new dynamometer devised by Professor Rowland of this University. A description of this new and useful piece of apparatus will be published shortly. The stimulating electrodes were placed upon the forehead and were of a special pattern, being so constructed as to remain moistened with glycerine during the entire period. It is hoped in the near future to carry out a complete series of determinations with this apparatus, using a number of individuals, and when this is done, a more careful description of the method will be published. The matter is referred to here only incidentally for the purpose of showing that the author's sleep curve belongs apparently to the general type described by Kohlschütter, however much it may be found to vary in details.

THE CAUSE OF SLEEP.

Numerous theories of sleep have been proposed in modern as in ancient times. Among recent theories, those published by Cajal* and Duval† have, at least, the advantage of novelty. According to the former, the neuroglia cells in the molecular layer of the cortex expand between the communicating processes of the cell units and act as an insulating medium to interrupt physiological conductivity and bring on the unconsciousness of sleep. Duval advances the simpler theory that conductivity is broken by the withdrawal of the cell processes from each other by amœbiform contraction, conductivity being

* Ramon y Cajal, *Archiv f. Anat.* (*u. Physiol.*), 1895, p. 375.
† Duval, *Comptès rendus de la soc. de Biol.*, Feb., 1895.

re-established upon awaking, or because of sensory stimulation, by the processes again elongating and intermingling. Theories of this kind are merely immediate speculative applications of anatomical facts. They can scarcely command serious attention unless supported by observations that indicate the possibility of such movements occurring. One may ask, for instance, whether conductivity is interrupted in the retina, the cord and the peripheral ganglia in the same way.

The general conception underlying most of the recent physiological theories of sleep seems to be that it is owing primarily to a fatigue of the elements of the central nervous system, and efforts have been directed toward explaining the immediate cause of this fatigue and the means by which the irritable condition of the nerve tissue is restored. Obersteiner,* for example, supposed that in the brain, as in the muscular tissue, functional activity is accompanied by the production of acid, which is not removed by the blood as rapidly as it is formed, and therefore accumulates and finally brings on fatigue, that is, lack of irritability, which is apparent to us as the condition of sleepiness. If the amount of acid is sufficient, sleep may occur involuntarily. Preyer† advocates a similar theory and specifies the lactic acid produced in muscular and nervous activity as the immediate cause of the occurrence of sleepiness, and its removal as the underlying fact of the recuperative effects of sleep. Pflüger‡ seeks the cause of fatigue in a different factor, namely, in the consumption of the supply of intra-molecular O stored in the nerve substance. During waking hours continuous functional activity is accompanied by katabolisms in which the O appears in the form of CO_2. The steady consumption of the stored O is not compensated by an equivalent absorption of O, and as a consequence the irritability of the nerve tissue runs down. Sleepiness is the result, and upon the withdrawal of external stimuli this passes normally into sleep, that is, the katabolisms in the brain cells cease, or, at any rate, sink below the level necessary to arouse consciousness. The very long rest which

* Obersteiner, *Allgemeine Zeitsch. für Psychiatrie*, xxix, p. 224, 1872-3.
† Preyer, *Centralblatt f. d. med. Wiss.*, xiii, p. 577, 1875.
‡ Pflüger, *Archiv f. die gesammt. Physiol.*, x, p. 468, 1875.

ensues, the period of normal sleep, would seem to be longer than is necessary to restore the adequate amount of combined oxygen, and Pflüger accounts for this delay upon the assumption of an inertia in the molecules of the nerve substance that must be overcome to start again the decompositions of functional activity; but once the molecules are set into vibration, each molecular explosion acts as a favoring condition to successive explosions.

None of these theories have been accepted as entirely adequate. They are difficult of experimental verification, and, so far as the attempt has been made, the results are not favorable to the theories. Preyer attempted to show that injection or ingestion of lactates produces the phenomena of sleepiness, but was obliged to admit that the results are variable with different individuals. The same experiment in the hands of others has given such uncertain results as to make it probable that sleep cannot be explained solely by an accumulation of lactic acid or lactates in the central nervous system. With regard to Pflüger's theory, Hill and Nabarro* have shown that the gaseous exchange in the brain is slight compared with that in the muscular tissue, and while this fact does not disprove the view that in the brain the oxygen consumption outruns the oxygen absorption, it at least tends to throw some doubt upon such an assumption. The exchange is not so great, normally, as to seriously alter the oxygen capacity of the blood streaming through the brain.

In normal sleep, moreover, we have to consider a phenomenon that appears with more or less suddenness and involves more or less completely and nearly simultaneously all the parts of the organ of consciousness quite independently of the degree to which these parts have been worked during the waking period. To take a concrete example, there can be no doubt that an individual who had passed an entire day without excitation of the centres of taste or smell might enjoy a sound sleep in which these centres would share. Normally, these centres are in activity only for short periods, yet during sleep they participate in the general loss of irritability of the cortex, perhaps to an even greater extent than the rest of the cortex, as it is an

* Hill and Nabarro, *Journal of Physiology*, xviii, p. 218, 1895.

interesting fact that dreams involving sensations of taste or smell are very unusual. It can hardly be supposed that these centres are fatigued from local production of acid or consumption of oxygen, and to account for their sleep upon the theories under discussion it would be necessary to assume that they had been robbed of their oxygen to supply other parts, or that the acid formed in other tissues had been transported to them. Neither of these theories seems to explain satisfactorily the common and nearly simultaneous loss of consciousness in all parts of the cortex.

A second group of theories has attempted to prove a relationship between the supply of blood to the brain and sleep. There has been an increasing amount of evidence within recent years to show that there is a lessened flow of blood through the brain during sleep. This has been shown by direct observations upon the exposed brain (Durham) or upon animals with a glass window in the skull (Donders, Durham), by the observations of Mosso and others, which have shown a diminution in volume of the brain during sleep in patients with defects in the skull, by observations upon the retinal circulation during sleep; and lastly, it follows apparently as a logical conclusion from recent experimental work on lower animals and plethysmographic observations on man, the tendency of which has been to show that a fall of blood pressure occurs during sleep. This fact, indeed, seems to be safely established. Whether there is really a lessened volume of blood in the brain or only a lessened blood flow need not be discussed here. The main point is, that the volume of blood circulating through the brain in a unit of time is lessened; there is a condition of cerebral anæmia. By some authors the anæmia has been regarded as a causal factor in the production of sleep, but in most cases it has been explained as a result of sleep, the cessation of functional activity being followed by a diminished blood supply.

The explanation which the author has been led to give to the plethysmographic curves, described in this paper, has suggested to him a theory of sleep that, in some of its features at least, is new. This theory may be stated briefly as follows: The immediate cause of normal sleep lies in a vascular dilatation (of the skin) that causes

a fall of blood pressure in the arteries at the base of the brain, and thereby produces an anæmic condition in the cortex cerebri. This condition of anæmia, in connection with the withdrawal of external stimuli, causes a depression of the psychical processes in the brain cells below the threshold of consciousness. The fall of blood pressure is due, in the first place, to a relaxation of tone in that portion of the vaso-motor centre controlling the skin vessels. The immediate cause of normal awaking, on the contrary, is found in the augmented flow of blood to the brain that follows upon the gradual constriction of the skin vessels as the vaso-motor centre recovers its tone. The periodicity of sleep is therefore directly connected with a rhythmic loss and resumption of tone in the vaso-motor centre. Throughout the waking period the vaso-motor centre is under continual stimulation, and is therefore in continual activity. Sensory impulses, especially from the skin and the cutaneous sense organs, are at all times falling into the central nervous system in greater or less quantities, and through a reflex pressor action on the vaso-motor centre these sensory impulses keep up a constant activity of the centre, particularly of that part controlling the skin vessels, as is indicated by the striking effect of such stimuli upon the volume of a limb when measured plethysmographically. Mental activity in all its forms is accompanied by a similar pressor effect upon the vaso-motor centre, which is likewise known to affect the skin circulation. During the waking hours, therefore, the vaso-motor centre is in uninterrupted activity, and the result must be the production of a condition of fatigue in this centre proportionate to the amount of stimulation. If the fatigue is sufficiently pronounced, the centre will relax and sleep ensue in spite of even strong sensory or mental stimuli. If the fatigue is less marked, as is normally the case at the end of a waking period, adequate relaxation takes place only after the withdrawal of sensory and mental stimuli, and our voluntary preparations for sleep consist essentially in devices to minimize these stimuli. That the vaso-motor centre is susceptible to fatigue, the author has shown to his own satisfaction by experiments consisting in the continuous stimulation of sensory nerves (sciatic), in curarized and narcotized animals. The great rise of blood

pressure that results from such stimulation soon passes off more or less completely, and that this result is owing to fatigue of the centre rather than to fatigue of the muscles in the walls of the blood-vessels is indicated by the fact that the blood-vessels in the ear of a rabbit may be kept in a condition of strong contraction for a long period (over an hour at least) by constant tetanic stimulation of the peripheral end of the cervical sympathetic nerve.

In addition to the effect of the cerebral anæmia, an accessory favoring condition to the production of sleep may be found in a certain degree of fatigue of the parts of the brain mediating psychical processes. Portions of the sensory and the association areas of the cortex, using Flechsig's nomenclature, must be active during the greater part of the waking period, and probably, therefore, lose their irritability to a greater or less extent. Upon the withdrawal of the normal blood supply, their irritability will tend to fall more quickly below the threshold of consciousness in consequence of this fatigue. We might, therefore, say that three factors combine to produce normal sleep: 1. A diminution of irritability, caused by fatigue, of large portions of the cortical area. 2. Voluntary withdrawal of sensory and mental stimuli involved in the preparations for sleep. 3. A diminished blood supply to the brain, owing to a relaxation of tone in the vasomotor centre and the fall of general arterial pressure thereby produced. The last factor is the immediate cause of sleep and explains its comparatively sudden and nearly simultaneous occurrence over the entire cortex. The relative importance of these three factors will vary, naturally, with attending circumstances. It would seem that the third condition must always precede sleep, and that, under normal relations, it is the determining element in the production of the unconsciousness of sleep. A combination of the 2nd and 3rd factors is probably adequate to cause sleep without preceding fatigue of the central nervous system. This probability is indicated by many facts in ordinary experience, such, for example, as the sleepiness felt when quietly resting after a heavy meal—the fall of blood pressure in this case following upon a dilatation in the splanchnic area. Perhaps a better instance is the often-quoted case of Strümpell's. In this case

a boy whose only avenues of sensory communication with the outside world were the right eye and the left ear could be sent to sleep at any time by bandaging the eye and stopping up the ear. On the contrary, the normal condition of sleepiness that makes itself distinctly felt to the individual and that follows upon healthy active exertion of body and mind is most probably connected with a genuine fatigue of the vaso-motor centre, particularly, I believe, of the part controlling the skin vessels. When in this condition, only strong sensory or mental stimuli are adequate to keep the centre in tone and prevent a fall of blood pressure, and if the fatigue is excessive, even such means fail and sleep ensues quite against the will.

The probability of a relationship between the supply of blood to the brain and the condition of sleep is indicated also by the phenomena preceding normal awaking. For some time before awaking the arm undergoes a gradual constriction, and in the half-hour or so just preceding awaking this constriction becomes comparatively rapid, bringing the arm at the time of awaking nearly or completely to its normal volume. Upon the explanation of the plethysmographic curve that has been adopted in this paper, these changes would mean that after a certain period of relaxation the vaso-motor centre gradually regains its tone, the resumption being more rapid shortly before awaking. The result of this process is to force a greater and greater supply of blood through the rested brain until finally the threshold of consciousness is overstepped and spontaneous awaking occurs. It is probable that under ordinary conditions awaking is almost always accelerated by the effect of some accidental external or internal stimulus. At the same time it must be admitted that if such stimuli were removed spontaneous wakening would eventually follow the gradually increasing vascular tone. It is an interesting fact that in the plethysmographic curves taken by the author there was always a marked constriction of the arm at the moment of final awaking. As the subject awoke he could see the pen rising rapidly upon the kymograph. The effect in this case seemed to be analogous to that caused by mental activity. The sudden increase in mental processes coincident with the access of full

consciousness acted as a stimulus to the vaso-motor centre, and the constriction produced was sudden and marked. Subsequently the pen again sank a certain distance, remaining finally at a level approximately the same as that shown at the time of going to sleep.

It frequently happened that during these experiments the subject awoke one or more times during the night. When the awaking was of the kind that brings full consciousness, it was accompanied by a marked constriction of the arm. In some cases, however, the awaking, although simultaneous with a sharp constriction of variable extent, was not followed by a permanent rise of the curve, the arm remained dilated to a much greater extent than was the case at the final awaking. Usually, if not always, in such cases the awaking was of the character that leaves the subject still drowsy; the eyes were kept closed and sleep soon returned. The incomplete extent of the return of consciousness in these cases is indicated by the facts mentioned on page 317. The subject, although awake and conscious of his surroundings, was certainly not fully awake, as he was mentally incapable, apparently, of recognizing distinctly his obligations to inform the watcher of his condition. This state of incomplete return of consciousness occurring during sleep is more or less familiar to every one. The effect upon blood pressure varies—in some cases it may apparently be slight or absent altogether—and this doubtless explains the quick relapse into the sleeping condition that usually follows. That consciousness may return temporarily without apparently any permanent increase in the flow of blood to the brain is an interesting fact that seems at first sight to be opposed to the views of the causation of sleep adopted in this paper, although the contradiction is only apparent. The usual relationship between the amount of blood flow and the intensity of the conscious processes does not at all exclude the possibility that changes sufficient to arouse consciousness may be produced in the brain cells by stimuli other than those implied in an augmented flow of blood. The phenomenon under consideration occurred usually after the intensity of sleep had passed its maximum and when the irritability of the nerve cells might be supposed to have returned nearly to the normal condition. Under these cir-

cumstances it may be conceived that the metabolic processes within the cells might be increased by internal causes of some kind and thus pass the threshold of consciousness, or that temporary sensory stimuli from without might produce a similar effect by direct effect on the cortical cells, and the conscious processes thus evoked might persist longer than the corresponding vaso-motor change. The point which the author is seeking to emphasize in his views upon the causation of sleep is that when internal or external causes, that in themselves are capable of exciting consciousness in the rested brain cells, are excluded, an augmented flow of blood to the brain may alone be sufficient to raise metabolism over the threshold of consciousness, and that this change is in fact the normal means provided to restore consciousness to the sleeping brain.

Some interesting suggestions arise from a comparison of the curve of intensity of sleep with the plethysmographic curve, assuming that the latter has been correctly interpreted in its bearings upon the circulation in the brain. This comparison has been made on page 328. One striking fact is, that during the period of increasing intensity of sleep there is a corresponding increase in the anæmic condition of the brain, the two conditions reaching their maxima apparently about the same time. If the normal appearance of the unconsciousness of sleep is owing immediately to the anæmic condition of the cortex, we can understand why the intensity of sleep should grow rapidly deeper after the threshold is passed, since the condition of anæmia becomes more pronounced in correspondence with the slow relaxation of tone in the vaso-motor centre. This increase in the intensity of sleep is not easily understood upon the theories of Obersteiner or Pflüger, and perhaps is more difficult of explanation upon the histological theories of Cajal and of Duval. It is impossible to say whether the maximum intensity of sleep corresponds exactly with the maximum anæmia of the brain. All that can be asserted is that during the first hour or so of sleep the two curves run a parallel course, as does also the curve of fall in temperature of the brain determined by Mosso. In their subsequent course, however, the plethysmographic curve and the intensity curve diverge widely. While the intensity curve returns rapidly to-

ward the threshold, the anæmia of the brain remains practically maximal during several hours, and gives place finally to a gradual increase in the blood flow as the vaso-motor centre recovers its tone. It thus happens that between the second and third hours after the beginning of sleep the intensity of sleep (according to Kohlschütter's curve) is but slightly below the threshold, while the anæmia of the brain is still maximal or nearly so. This divergence in the two curves may be explained, perhaps, on the assumption that the cells of the cortex regain their normal irritability more rapidly than those of the vaso-motor centre, being less fatigued or possessing a more active metabolism. At the time mentioned the brain cells are practically in a condition to awake, but their metabolism is kept below the threshold solely, perhaps, by the anæmic condition of the brain.

Attention has often been called to the fact that the curve of intensity of sleep does not explain the greater recuperative effect of a long slumber as compared with a short one. According to the intensity curve, the brain should be nearly completely rested after a sleep of three hours, whereas our experience seemingly proves the reverse. This apparent difficulty is explained by the plethysmographic curve; for after a sleep of three hours the vaso-motor centre is still in a condition of depressed irritability, and if awaking occurs at that time, this centre is stimulated to activity while still in a condition of fatigue. The usual long duration of sleep may be referred then to a slow recovery from fatigue on the part of the vaso-motor centre. We may suppose, indeed, that the actual beginning of sleep, its duration and normal awaking are directly connected, under ordinary circumstances, with the condition of the vaso-motor centre. Were it not for the long relaxation of this centre the cortical cells would probably enter into activity at a much earlier period than normally occurs, and would therefore be deprived of the benefit of a long rest. According to this view, the normal periodicity of sleep, which is its most characteristic phenomenon and the one most difficult of explanation upon previous theories, is to be referred finally to the characteristics of the vaso-motor centre.

In conclusion it should be stated that although the above-described

theory of sleep was arrived at independently by the author from a consideration of the results of his experiments, a survey of the literature shows that the same general idea has been suggested at various times by other investigators. Mosso* speaks of having at one time believed in a mechanical theory of sleep, according to which awaking was caused by blood being forced from the extremities toward the brain. His subsequent extensive and most interesting work caused him to abandon this theory as superficial and insufficient. Certainly no one is better qualified from wide experience with the subject to speak authoritatively upon the physiology of sleep, but after a careful study of Mosso's published works, so far as they have been accessible to me, I fail to find any convincing facts that oppose the vaso-motor theory. Mosso holds to the view of an independent regulation of the brain circulation through intrinsic vaso-motor fibres, a theory that is quite opposed to recent experimental work on lower animals. It seems also to the author that this distinguished investigator, particularly in his work on the temperature of the brain, looked for a sudden change of some character to mark the moments of sleep and awaking, whereas the passing of the threshold of consciousness in either direction may obviously occur without sudden circulatory or temperature changes, although such changes are apparent enough if considered in relation to the entire period of normal sleep.

De Boeck and Verhoogen† speak of a theory by Heger, according to which a necessary condition of sleep is a depression of vascular tone. If I understand the authors correctly, this theory was announced in Professor Heger's lecture, and not in a published communication. It is coupled with a suggestive reference to the differences in the circulation in the cortex and the base of the brain depending upon the different resistances on the two paths. This point is elaborated in the paper by De Boeck and Verhoogen. They state that the arterial branches from the circle of Willis supplying the basal ganglia are numerous, generally arise at a right angle, and are large and short, while those

* Ueber den Kreislauf des Blutes im menschlichen Gehirn, p. 75, 1881.

† De Boeck and Verhoogen, Contribution à l'étude de la circulation cérébrale. *Journal de Médecine de la Société royale de Bruxelles*, 1890.

destined for the cortex are smaller, longer and more tortuous. For this reason, under any given pressure in the circle of Willis, more blood will take the shorter, less resistant path to the basal ganglia. When, therefore, blood pressure is lowered, the anæmia of the cortex will be relatively greater than in the basal portions of the brain, and it may be supposed that with a certain low pressure the flow through the cortex may cease, while in the basal portion a circulation still persists. This idea is valuable in indicating a means by which the irritability of the cortex may be suspended by a moderate fall of arterial pressure, while that of the medullary centres, for example, may remain. In how far the basal portions of the brain are affected by sleep has not been demonstrated as yet. Some incomplete observations by Tarchanoff indicate that the spinal cord, when severed from the brain, shows as rapid a reaction time during sleep as in the waking hours. So, too, the familiar instances of individuals walking in their sleep show that the power of muscular co-ordination and locomotion may be associated with the unconsciousness of sleep.

In a work recently published by Hill,* that has appeared since my researches were completed, he advocates the theory that sleep depends on an anæmia of the brain brought about by relaxation in tone of the splanchnic area. The anæmia is produced, he believes, both by a fall in general arterial pressure and by a corresponding rise in general venous pressure, the latter factor tending to retard the flow of blood through the brain. Hill sums up his opinions in the metaphorical statement that "The vaso-motor centre is the hub round which turns the wheel of a man's active mental life." From my own observations and from those of Mosso, I cannot help believing that Hill is in error in supposing that the fall of arterial pressure occurring during sleep is primarily owing to a relaxation of tone in the splanchnic area. (The reasons for this conclusion have been stated on page 324 and need not be repeated here.) It is difficult to obtain positive evidence of the condition of the splanchnic circulation during normal sleep. So far as the author knows, no such evidence is in our pos-

* Hill, The Physiology and Pathology of the Cerebral Circulation. London, 1896.

session at present. On the contrary, our evidence as regards the condition in the skin seems to be decisive and capable of easy demonstration. When vascular dilatation does occur in the splanchnic area, it should lower blood pressure unless compensated by vascular constriction elsewhere; and in so far as it lowers blood pressure, should facilitate the production of sleep. The well-known sleepiness arising after a heavy meal, when the digestive organs are in functional dilatation, is an example of this effect. Dilatation in either the skin area or splanchnic area, or both, would suffice to fulfill the mechanical conditions of blood flow necessary to sleep; it is simply a question of where this dilatation takes place in normal sleep.

In the theory of sleep proposed in this paper it is assumed that the quantity of blood flowing through the brain in some way controls the amount of psychical activity. This idea seems to be at variance with accepted physiological conceptions of the relations between blood flow and functional activity in other organs of the body. With regard to the skeletal muscles, and many of the glands whose metabolism is directly controlled by peripheral nerves, it has been shown that mere increase of blood supply is not alone sufficient to arouse functional activity, and that under appropriate stimulation these tissues may continue to exhibit functional activity for a certain time after the blood supply is entirely cut off. It must be borne in mind, however, that all the tissues do not behave alike in this respect. In the kidney, for example, we have an organ that, unlike the sweat glands, the cilia or the skeletal muscles, is extremely sensitive to variations in the blood supply. When the volume of blood flowing through this organ falls below a certain level, secretory activity is suspended and, within limits, the amount of functional activity varies with the quantity of blood. The precise way in which the augmented blood flow increases the secretory activity is not known, but there can be little doubt that the effect is in the nature of a direct stimulus to the functional metabolism of the secretory cells.

In the brain the conditions are much more complex, and our knowledge of the effects of varying conditions is much less direct. The cells of the cortex cerebri are in manifold connections with other parts

of the nervous system, and are therefore under frequent stimulation from impulses falling into them from without. But in addition to this factor, the evidence we possess seems to show that the irritability of these cells is directly influenced by the amount of the blood supply. When the latter falls below a certain level the irritability of the cells is correspondingly diminished, and external stimuli from other nerve units must be proportionately increased to arouse psychical activity. If the volume of blood is diminished to a still greater extent, even the strongest external stimulation fails to arouse functional activity. Unconsciousness is known to follow almost immediately in man from compression of the carotids, from failure of the heart beat, or from other conditions causing a sudden diminution in the blood supply to the brain. In some recent experiments made by Broca and Richet,* in which the excitability of the cortex (in the dog) was determined by direct stimulation of the motor region, it is stated that the excitability disappeared completely within thirty seconds after shutting off the circulation to the brain by clamping the arteries. The unconsciousness thus produced is not, of course, normal sleep, but its occurrence under the conditions described indicates that the great diminution in blood supply to the brain that does happen during sleep is one of the essential factors in the causation of the more or less pronounced unconsciousness of sleep. Whether the relation of the blood supply to the functional activity of the cortical nerve cells depends upon some single factor, such as the supply of oxygen or the removal of carbon dioxide, or whether it is much more complex, involving other nutritive changes and perhaps conditions of pressure, cannot be discussed profitably at present, owing to the lack of experimental data.

DESCRIPTION OF PLATE XXXI.

Fig. 1.—Plethysmographic record of hand and lower part of fore-arm, on the right side, taken on the night of July 25th, 1895. The watcher was Dr. G. T. Kemp. A fall in the curve indicates dilatation of the arm, and a rise, constriction. On the previous night only about three hours of sleep had been obtained, owing to an unsuccessful attempt at a similar experiment. On the day of the experiment (July 25th) had taken a long journey, partly

* Broca and Richet, *Comptes rendus de la Soc. de Biol.*, Feb. 12, 1897.

by water and partly by rail. As nearly as could be determined, was asleep about 1 A. M. A fall of 1 mm. in the record corresponds to an increase of 0.37 cc. in the volume of the arm. At 2.45 A. M., two hours after the beginning of the experiment, the dilatation of the arm was equal to 18.5 cc. The subject of the experiment awoke finally, shortly after 5.30, the moment being marked on the record by a ×. The arm contracted rapidly and subsequently fell slowly. The subject remained in the apparatus for another half-hour, talking with the watcher, the arm retaining a fairly constant volume which was greater than that at the moment of going to sleep. The sharp upstroke at the end of the experiment was purposely made by moving the hand in the plethysmograph, with the object of ascertaining the position of the time pen with regard to the pen of the plethysmograph recorder. From 2.57 to 3.07 the notes of the watcher record that the sleeper was probably awake, was uneasy, shifting his position frequently and sighing. The series of sharp oscillations at this period are probably accounted for by these movements. The sharp rise at 1.17 was coincident with a jerk of one of the feet and a change in position; the rise just beyond 1.45 was coincident with a change of position, a deep sigh and a movement of the plethysmograph arm; at 2.33 the notes record several twitches of foot, several deep sighs, drawing up of both feet; the large rise just after 4 A. M. occurred while the watcher was out of the room; at 4.24 the notes record "uneasy, sighs, nothing to account for the great rise of the curve"; at 4.38, "shifts position, sighs, great rise in curve"; at 5.10, "sighs, shifts position, curve drops and then rises rapidly." The character of the record here is such as to indicate a movement of the hand within the plethysmograph, thus accounting for the first sudden drop of the curve; at 5.22, "has been perfectly quiet, breathing regularly but not deeply, two abrupt and considerable rises have occurred on the curve"; at 5.35, "sighs, shifts position, rubs his eyes but does not open them"; at 5.37, "awakes suddenly and asks the time," this is the point marked ×. Throughout the record there are numerous notes of changes in position, sighs, noises happening simultaneously with the oscillations in the curve. The parts of the notes reproduced above refer to the most noticeable of these oscillations.

Fig. 2.—Plethysmographic record of hand and lower part of fore-arm, on the right side, taken on the night of September 17, 1895. The watcher was Dr. Reid Hunt. A fall in the curve indicates dilatation of the arm, and a rise, constriction. On the previous night the subject of the experiment had sat up until 3 A. M. and slept from 3 to 6 A. M. As nearly as could be determined, was asleep by 1.37. A fall of 1 mm. in the curve indicates an increase in the volume of the arm of 0.37 cc. At 2.12, 50 minutes after the beginning of the experiment, the dilatation of the arm was equal to 15.91 cc. At 5.45 the sleeper awoke suddenly, at the point on the curve marked ×. After the sharp constriction of the arm, which was observed by the subject of the experiment while it was taking place, there was a slow dilatation, which was followed by a second permanent rise to a level corresponding to that near the beginning of the experiment before sleep appeared. At 4.18 and at 4.59, according to the notes of the watcher, the subject awoke and gave the signal agreed upon, the work "awake"; at each point there is a sharp rise of the curve. The period of consciousness was very brief, sleep soon coming on. The notes of the watcher in this case are brief and may be given entire.

1.22, lights lowered, experiment begun. 1.30, large rise in curve, coincident with sneeze on the part of the watcher. 1.31, movements of sleeper. 1.35, loud talking and disturbance in the street. 1.48, sighs, 1.50, sighs. 1.58, deep breath. 2.09, deep breath. 2.12, kicks the foot. 2.20, movement of free hand toward plethysmograph, legs drawn up, simultaneously the large rise on the curve just before the mark 2.22. 2.36, movements of the legs, large rise in the curve. 2.42, cab drove by. 2.50, movements of legs. 3.03, movements of legs. 3.12, slight movement. 3.20, deep breath, movements. 3.25 and 3.34, movements. 3.38 and 3.45, movements of legs. 3.52, very quiet. 3.54, cab in the street. 4.02, 4.13 and 4.16, movements of the legs. 4.18, sleeper calls out "awake." 4.37, very quiet. 4.59, sleeper spoke. 5.06, sleeper moved and rubbed his eyes. 5.15, moved and rubbed his eyes. 5.18, moved and rubbed his eyes. (The sleeper after the experiment could not recall being conscious at these times.) 5.45, awoke and began to converse.

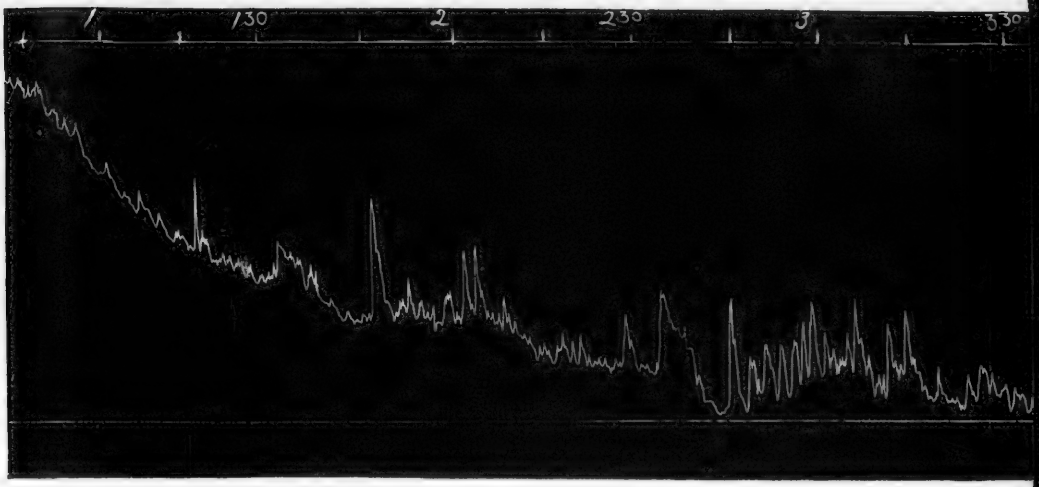


FIG. 1.

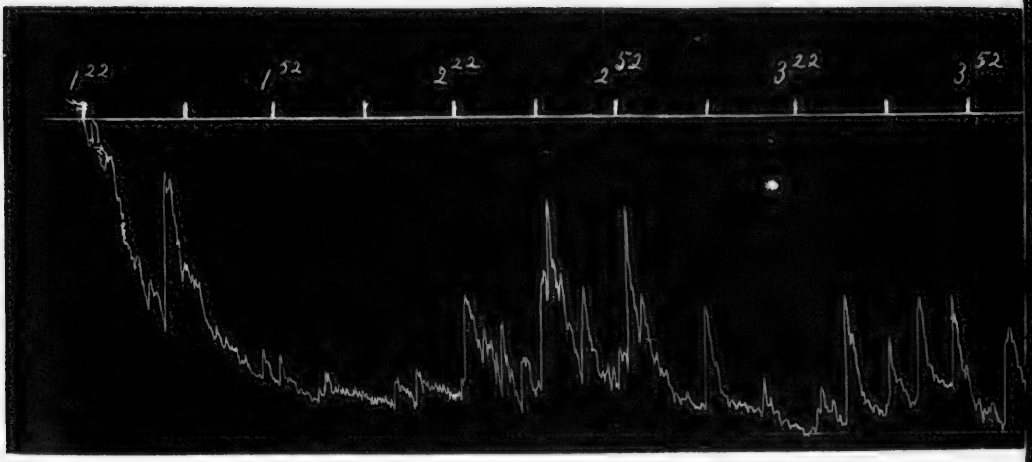
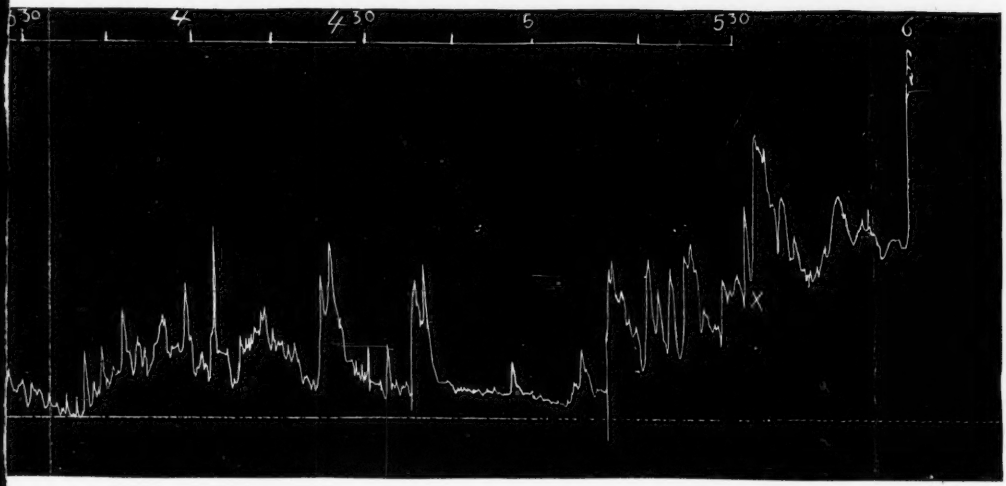
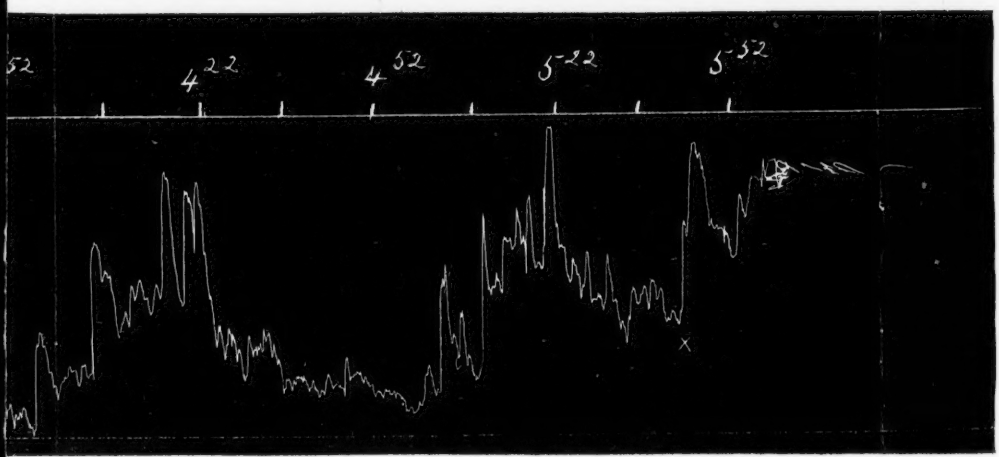


FIG. 2.



G. 1.



IG. 2.

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